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(54) Title: HUMAN BREAST AND OVARIAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES

(57) Abstract

This invention relates to newly identified breast, ovarian, breast cancer and/or ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, particularly disorders of the breast and/or ovary, including the presence of breast cancer and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, particularly disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

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Human Breast and Ovarian Cancer Associated Gene Sequences and Polypeptides

Field of the Invention

This invention relates to newly identified breast, ovarian, breast cancer, and ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, specifically disorders of the breast or ovary, particularly the presence of breast and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

Background of the Invention

Breast cancer represents the most frequent cause of early morbidity and mortality in women in North America (Harris et al, New Eng. J. Med. 327:319, 390 and 473 (1992)). It is generally believed that this malignancy arises from a multi step process involving mutations in a relatively small number of genes, perhaps 10 or less. These mutations result in significant changes in the growth and differentiation of breast tissue that allow it to grow independent of normal cellular controls, to metastasize, and to escape immune surveillance. The genetic heterogeneity of most breast cancers suggests that they arise by a variety of initiating events

and that the characteristics of individual cancers are due to the collective pattern of genetic changes that accumulate (Harris et al. New Eng. J. Med. 327:319, 390 and 473 (1992)).

The classes of genes that are involved in breast cancer are not unlike those found in a number of other well characterized malignancies, although some are highly specific for breast cancer. In particular, mutations in the genes that encode receptors involved in binding to estrogen and progesterone are particularly important because they likely cause the breast cells to proliferate while rendering them unresponsive to the antitumor effects of these hormones in advanced malignancy. In addition, changes in the genes that encode growth factors, other receptors, signal transduction molecules, and transcription factor molecules are frequently involved and have alterations that are involved in the development and progression of breast cancer (King, Nature Genetics 2:125 (1992)). The characterization of the type and number of mutations seen in individual breast cancers is useful in classifying the biological properties of individual cancers and in determining the prognosis for individual patients. For example, the erbB2/HER2/neu gene is particularly valuable in predicting the prognosis of both node-positive and node-negative patients based on the amplification status of the gene (King, Science 250:1684 (1990)). Several additional members of this family have been discovered but the ligand for erbB2/HER2/neu remains unknown. It is anticipated that further advances in therapeutics will be achieved by the development of therapies that disrupt aberrant growth signaling pathways or affect the cellular interactions of breast cancer cells with native stroma or metastatic sites.

Although oncogenes are likely to be very important in breast cancer, tumor suppressor genes may also play an important role. Certain of these genes, including p53 and Rb-1, are essential to the normal mechanisms that control cell cycle events, especially those checkpoints at the border of the different stages of the cell cycle (Hollstein et al, Science 253:49 (1991); Srivastava et al, Nature 348:747 (1990)).

In 1969, Li and Fraumeni documented a familial cancer syndrome that had an autosomal dominant pattern of expression (Li et al, Ann. Intern. Med. 71:747 (1969)). Members of these families had sarcomas, breast cancers, brain tumors, leukemias, adrenocortical carcinomas, and other malignancies. Family studies demonstrated that the gene responsible for the syndrome was located on chromosome 17, and examination of the p53 gene as a candidate gene revealed that this gene was mutated in five families (Malsin et al, Science 250:1233 (1990)). In the last two years, two genes linked to familial breast cancer,

designated BRCA1 and BRCA2, have been isolated and characterized. BRCA1 is at 17q21 (Claus et al, Am. J. Epidemiology 131:961 (1990); Hall et al, Science 250:1684 (1990); Easton et al, Am. J. of Human Genetics 52 (4):678 (1993); Black et al, Am. J. of Human Genetics 52 (4):702 (1993); Bowcock et al, Am. J. of Human Genetics 52 (4):718 (1993); Miki et al, Science 266:66 (1995)). The demonstration of loss of heterozygosity (LOH) at 17q25 has defined another potential tumor suppressor gene (Lindblom et al, Human Genetics 91:6 (1993); Cornelis et al, Oncogene 8:781 (1993); Theile et al, Oncogene 10:439 (1995)).

There is a need, therefore, for identification and characterization of such factors that modulate activation and differentiation of breast and ovarian cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

The present invention relates at least in part, to a novel breast and ovarian and breast and ovarian cancer related polynucleotides and polypeptides. The discovery of these breast and ovarian cancer related polynucleotides provides new compositions which are useful in the diagnosis, prevention and treatment of disorders of the female reproductive system, particularly of the ovary including, but not limited to ovarian cancer, and the breast, including but not limited to breast cancer.

Summary of the Invention

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 418) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a breast, ovarian, breast cancer, and/or ovarian cancer polypeptide. The present invention further includes breast, ovarian, breast cancer, and/or ovarian cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid

sequences comprising, or alternatively consisting of, breast, ovarian, breast cancer, and/or ovarian cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 419 to 836) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention. Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the female reproductive system, specifically disorders related to the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention.

Detailed Description

Tables

Table 1 summarizes some of the breast/ovarian cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the breast/ovarian cancer polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence

segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence.

Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the breast, ovarian, breast cancer or ovarian cancer associated polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Breast, ovarian, breast cancer and/or ovarian cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most breast, ovarian, breast cancer and/or ovarian cancer associated polypeptide sequence shown in the Sequence Listing.

Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be

"isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID, from which library it came and in which ATCC deposit the library is contained. Furthermore,

it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made persuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a breast/ovarian cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF)

encoded by polynucleotide SEQ ID NO:X. There are 418 breast/ovarian cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:418). Likewise there are 418 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:419 through SEQ ID NO:836). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In otherwords, since there are 418 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can be determined by the formula X + 418 = Y. In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation,

hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to

a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the breast/ovarian cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See

generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Breast, Ovarian, Breast Cancer and Ovarian Cancer Associated Polynucleotides and Polypeptides of the Invention

It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human breast, ovarian, breast cancer and/or ovarian cancer tissues. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer as more fully described below.

Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotides and the polypeptides encoded thereby.

Table 1

Seq ID No.	Sequence/ Contig ID	Gene Name	Overlap	HGS Nucleotide Start	HGS Nucleotide End	% Identity	% Similarity	Clone ID
1	419266	monoamine oxidase B [Homo sapiens] >gi|187376 monoamine oxidase B [Homo sapiens] >bbs|134021 monoamine oxidase B, MAO B [human, platelet, Peptide Partial, 520 aa] [Homo sapiens] >pir|JH0817|JH0817 amine oxidase (flavin-containing) (EC 1.4.3.4) B - human >	gi|187359	2	1021	95	95	HAGFP75
2	429114			51	383			HATDC43
3	506777			51	233			HRGCY74
4	508678	(AF059293) cytokine-like factor-1 precursor [Homo sapiens] >sp|O75462|O75462 CYTOKINE-LIKE FACTOR-1 PRECURSOR. Length = 422	gi|3372627	3	155	100	100	HFIJG81
5	508968	DNA helicase [Homo sapiens] >pir|A58836|A55311 DNA helicase RECQL - human Length = 659	gi|619863	2	739	95	96	HHTLH91
6	509029			770	1096			HLMDG72
7	519726			359	529			HCSSB83

8	522632			3	299			HRGBG45
9	524655			522	686			HUSGS36
10	525847	glyoxalase II [Homo sapiens] >sp|Q16775|GLO2_HUMAN HYDROXYACYLGLUTATHIONE HYDROLASE (EC 3.1.2.6) (GLYOXALASE II) (GLX II). Length = 260	gnl|PID|e1971 27	1	162	54	73	H6EDP14
11	530306			239	355			HCHCC28
12	532818	(AF035178) elongation factor 1 A2 [Oryctolagus cuniculus] >gi|38456 elongation factor 1 alpha-2 [Homo sapiens] >pir|S35033|EFHUA2 translation elongation factor eEF-1 alpha-2 chain - human >sp|Q05639|EF12_HUMAN ELONGATION FACTOR 1-ALPHA 2 (EF-1-ALPHA-2) (S	gi|3098311	43	441	95	95	HAMFD92
13	533385			1258	1827			HTWAO42
14	533532	actin capping protein alpha subunit [Homo sapiens] >gi|2393732 (AC002543) f-actin capping protein alpha-2 subunit [Homo sapiens] >sp|P47755|CAZ2_HUMAN F-ACTIN CAPPING PROTEIN ALPHA-2 SUBUNIT (CAPZ). >gi|433308 capping protein alpha [Homo sapiens] {SUB 3-2	gi|595255	18	947	95	95	HETCD42

15	534852	(AF041472) ataxin-2 [Mus musculus] >sp|O70305|O70305 SPINOCEREBELLAR ATAXIA 2 HOMOLOG (ATAXIN-2). Length = 1285	gi|3005020	3	869	77	77	HCE4Q55
16	537910	R kappa B [Homo sapiens] >pir|S52863|S52863 DNA-binding protein R kappa B - human >sp|Q15312|Q15312 R KAPPA B. Length = 1324	gi|695579	3	443	100	100	HTOAO52
17	538460			574	1026			HSSMY42
18	539577	transcriptional activator [Homo sapiens] >gnl|PID|d1005685 hSNF2b [Homo sapiens] >pir|S45252|S45252 SNF2beta protein - human >gi|4056413 (AC006127) SN24_HUMAN; nuclear protein GRB1; homeotic gene regulator; SNF2-BETA [Homo sapiens] {SUB 814-1474} Length =	gi|902046	1	540	89	89	HKADQ93
19	548379	complement protein C7 precursor [Homo sapiens] >pir|A27340|A27340 complement C7 precursor - human >sp|P10643|CO7_HUMAN COMPLEMENT COMPONENT C7 PRECURSOR. Length = 843	gi|179716	92	1336	92	92	HATCK25
20	548489	proteasome subunit HsN3 [Homo sapiens] >pir|S50147|S50147 multicatalytic endopeptidase complex (EC 3.4.99.46) beta chain N3 - human >sp|P28070|PRCB_HUMAN PROTEASOME BETA CHAIN PRECURSOR (EC 3.4.99.46) (MACROPAIN BETA CHAIN)	gnl|PID|d100 6192	3	857	99	99	HCGAF33

		(MULTICATALYTIC ENDOPEPTIDASE C						
21	548595	inosine monophosphate dehydrogenase type II [Homo sapiens] >gi|1702964 inosine monophosphate dehydrogenase type II [Homo sapiens] >pir|I52303|A31997 IMP dehydrogenase (EC 1.1.1.205) II - human >sp|P12268|IMD2_HUMAN INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE	gi|602458	971	1525	100	100	HTXEE92
22	549337	stromelysin-3 precursor [Homo sapiens] Length = 488	gi|456257	449	1081	96	96	HJMAF23
23	549777			54	293			HPMAC61
24	553091	pancreatic peptidylglycine alpha-amidating monooxygenase, PAM=membrane-bound isoform {alternatively spliced, clone PAM-3, transmembrane domain (Ba region)} [human, islet cell tumor cell line QGP-1, Peptide Partial, 971 aa] [Homo sapiens] >sp|Q16252|Q16252	bbs|159681	898	2598	97	97	HEMFU73
25	553827	B-CAM gene product [Homo sapiens] >pir|I37202|I37202 B-CAM protein - human Length = 588	gi|535179	2	388	80	80	HBHMI67

26	556350			263	655			HCHOC59
27	556351	'FKBP52; 52 kD FK506 binding protein' [Homo sapiens] >pir|A46372|A46372 immunophilin FKBP52 - human >sp|Q02790|FKB4_HUMAN P59 PROTEIN (HSP BINDING IMMUNOPHILIN) (HBI) (POSSIBLE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE) (EC 5.2.1.8) (PPIASE) (ROTAMASE) (FKBP5	gi|186390	2	1216	97	97	HE8DF57
28	557007	ubiquitin conjugating enzyme [Homo sapiens] >pir|A49630|A49630 ubiquitin conjugating enzyme - human (fragment) Length = 298	gi|388309	3	698	99	100	HTEJK85
29	558140	(AD001530) putative [Homo sapiens] >sp|G2335055|G2335055 XAP-5. >gnl|PID|d1012538 HXC-26 [Homo sapiens] {SUB 15-339} >gi|1203974 XAP-5 gene product [Homo sapiens] {SUB 66-339} Length = 339	gi|2335055	3	1070	71	71	HKAAM18
30	558456	adipocyte lipid-binding protein [Homo sapiens] >pir|A33363|FZHUF fatty acid-binding protein, adipocyte - human >sp|P15090|FABA_HUMAN FATTY ACID-BINDING PROTEIN, ADIPOCYTE (AFABP) (ADIPOCYTE LIPID-BINDING PROTEIN) (ALBP) (A-FABP). {SUB 2-132} Length = 132	gi|178347	69	332	100	100	HISBQ67
31	558708	N-cadherin [Homo sapiens] Length = 747	gi|416293	3	515	79	79	HSYBX61
32	574789			301	402			HLDNM79

33	578203			2	445			H6EDN57
34	585385	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir|A35954|A35954 endoplasmin precursor - human >sp|P14625|ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803	gi|37261	99	347	71	71	HOFMP70
35	588869	leukocyte adhesion glycoprotein precursor [Homo sapiens] Length = 1152	gi|307114	1	720	98	98	HDPFK39
36	597076	preferentially expressed antigen of melanoma [Homo sapiens] >sp|P78395|P78395 PREFERENTIALLY EXPRESSED ANTIGEN OF MELANOMA. Length = 509	gi|1903384	80	811	77	77	HETHE66
37	598656	sigma receptor [Homo sapiens] >gi|1916800 SR31747 binding protein 1 [Homo sapiens] >gi|2914740 (AF001977) type I sigma receptor [Homo sapiens] >pir|JC5266|JC5266 sigma receptor 1 - human >sp|Q99720|Q99720 SIGMA RECEPTOR. Length = 223	gi|1783387	3	587	100	100	HMEIY05

38	611880	Acetyl-CoA:acetyltransferase (EC 2.3.1.9) (Acetoacetyl-CoA thiolase). [Escherichia coli] >gi|1788554 (AE000311) acetyl-CoA acetyltransferase [Escherichia coli] >pir|F64992|F64992 hypothetical protein b2224 - Escherichia coli (strain K-12) >sp|P76461|ATOB_	gnl|PID|d1016745	1	108	100	100	HOVAS88
39	614329	ORF, HEIR-1; pot. neuroblastoma-associated regulator [Homo sapiens] >gi|395338 helix-loop-helix protein [Homo sapiens] >gi|512437 HEIR-1 [Homo sapiens] {SUB 30-148} Length = 148	gi|490013	300	755	86	86	HFPCQ02
40	616066			121	213			HSIGC05
41	620956	ribosomal protein S9 [Rattus norvegicus] >pir|JN0587|S21497 ribosomal protein S9 - rat Length = 194	gi|57143	3	473	95	97	HOFOB28
42	621889	unnamed protein product [unidentified] >gi|468550 CCT (chaperonin containing TCP-1) epsilon subunit [Mus musculus] >pir|S43061|S43061 t-complex-type molecular chaperone Ccte - mouse Length = 541	gnl|PID|e306129	16	423	95	97	HOFOC44
43	624017	(AB003732) polyubiquitin [Cricetulus griseus] >sp|O35080|O35080 POLYUBIQUITIN. >gi|4105408 (AF045474) polyubiquitin [Schistosoma mansoni] {SUB 694-988} Length = 1038	gi|2627133	1	1170	95	97	HMCBS12

44	651784	histone H2A.X [Homo sapiens] >pir|S07631|S07631 histone H2A.X - human >sp|P16104|H2AX_HUMAN HISTONE H2A.X. {SUB 2-143} Length = 143	gi|31973	2	514	98	98	HKGAI94
45	651826	keratin, 55K type II cytoskeletal - human (fragment) Length = 489	pir|B24177|B 24177	2	1300	86	86	HNTAH42
46	653282	phosphate transfer protein B precursor, mitochodrial - bovine Length = 361	pir|D53737|D 53737	30	392	90	90	HOFNY90
47	657122			1	204			IIKGAQ13
48	661442	rab1B protein (AA 1 - 201) [Rattus sp.] Length = 201	gi|57006	1	672	98	99	IICHMI33
49	664914	phosphotyrosyl phosphatase activator [Oryctolagus cuniculus] >pir|B54021|B54021 phosphotyrosyl phosphatase activator PTPA - rabbit >sp|Q28717|Q28717 PHOSPHOTYROSYL PHOSPHATASE ACTIVATOR. Length = 323	gi|509144	1	228	98	100	HEGAK11
50	666654			63	395			HOFNL37
51	667084	cytokeratin 17 [Homo sapiens] >gi|34075 keratin related product [Homo sapiens] >pir|S30433|S30433 keratin 17, cytoskeletal - human >sp|Q04695|K1CQ_HUMAN KERATIN, TYPE I CYTOSKELETAL 17 (CYTOKERATIN 17) (K17) (CK 17) (39.1) (VERSION 1). {SUB 2-432} Length	gi|30379	3	1379	100	100	HKADA74

52	667380	cell surface glycoprotein [Homo sapiens] >gnl|PID|d1006754 TALLA-1 [Homo sapiens] >gnl|PID|d1001976 cell surface glycoprotein [Homo sapiens] >pir|I39368|I39368 T-cell acute lymphoblastic leukemia associated antigen 1 - human >sp|P41732|A15_HUMAN CELL SURF	gnl|PID|d1001976	1	474	100	100	HMIBK53
53	669530			264	440			HPFCJ30
54	671315	cell cycle checkpoint control protein [Homo sapiens] >sp|Q99638|Q99638 CELL CYCLE CHECKPOINT CONTROL PROTEIN. Length = 391	gi|1765956	320	1279	92	92	HDABE95
55	671993	NAD(H)-specific isocitrate dehydrogenase gamma-subunit precursor [Homo sapiens] >gnl|PID|e219959 NAD (H)-specific isocitrate dehydrogenase gamma subunit precursor [Homo sapiens] >gi|1302655 NAD+-isocitrate dehydrogenase gamma subunit [Homo sapiens] >gi|40	gnl|PID|e211919	1	993	91	91	HSJCA89
56	674618			223	312			HOVBX22
57	675027			789	1160			HSDII69
58	677202	vimentin [Homo sapiens] >sp|Q15867|Q15867 VIMENTIN (FRAGMENT). Length = 354	gi|340232	705	896	100	100	HWACG51

59	678504	ORF YGR031w [Saccharomyces cerevisiae] >pir|S64322|S64322 probable membrane protein YGR031w - yeast (Saccharomyces cerevisiae) Length = 342	gnl|PID|e243277	320	640	38	63	HCHAG27
60	678985	54 kDa protein [Homo sapiens] >gnl|PID|e1245514 p54nrb [Homo sapiens] >pir|G01211|G01211 54 kDa protein - human >sp|Q12786|Q12786 54 KDA PROTEIN. Length = 471	gi|407308	358	1203	100	100	HCHOL54
61	682161	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi|3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp|O14745|O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi|2920585	3	869	89	89	HCHAG19
62	683476			1	132			HOFMM27
63	691146	KDEL receptor [Homo sapiens] >pir|S13293|S13293 KDEL receptor - human >sp|P24390|ER21_HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212	gi|34031	1	372	100	100	HDABB02
64	693589			1	393			HCHAS12

65	694991	B4B gene product [Homo sapiens] >gnl|PID|e265628 progression associated protein [Homo sapiens] >gi|1932786 epithelial membrane protein [Homo sapiens] >gi|2506160 TMP [Homo sapiens] >sp|P54849|EMP1_HUMAN EPITHELIAL MEMBRANE PROTEIN-1 (EMP-1) (TUMOR-ASSOCIA	gnl|PID|e194946	1	663	98	98	HRAAY77
66	698303	heat shock factor 1 [Homo sapiens] >pir|A41137|A41137 heat shock transcription factor 1 - human >sp|Q00613|HSF1_HUMAN HEAT SHOCK FACTOR PROTEIN 1 (HSF 1) (HEAT SHOCK TRANSCRIPTION FACTOR 1) (HSTF 1). Length = 529	gi|184403	23	1168	85	85	HSHCA55
67	698669	filamin [Homo sapiens] Length = 2647	gi|1203969	27	1274	98	98	HEGAR20
68	705696			321	458			HOFMP28
69	706393	vacuolar H+ ATPase proton channel subunit [Homo sapiens] >pir|A39367|A39367 H+-transporting ATPase (EC 3.6.1.35) chain PKD1 - human Length = 155	gi|189676	119	604	84	85	HSKHP64
70	707357			3	344			HOFMM35

71	707360	leucine aminopeptidase, LAP [cattle, kidney, Peptide, 513 aa] [Bos taurus] >pir|A54338|APBOL leucyl aminopeptidase (EC 3.4.11.1), renal - bovine >sp|P00727|AMPL_BOVIN CYTOSOL AMINOPEPTIDASE (EC 3.4.11.1) (LEUCINE AMINOPEPTIDASE) (LAP) (LEUCYL AMINOPEPTIDA	bbs|137417	1	447	81	89	HOFOF35
72	707375	serine/threonine protein kinase [Homo sapiens] >pir|S23385|S23385 protein kinase (EC 2.7.1.37) cdc2-related PCTAIRE-1 - human >sp|Q00536|KPT1_HUMAN SERINE/THREONINE-PROTEIN KINASE PCTAIRE-1 (EC 2.7.1.-). >sp|G252370|G252370 CDC2-RELATED PROTEIN KINASE {CL	gi|36619	2	1582	92	92	HTOJQ73
73	707754			2	376			HLDBT45
74	711172			237	395			HOVCI40
75	712248	transcription factor AP-2 beta [Homo sapiens] >sp|E286536|E286536 TRANSCRIPTION FACTOR AP-2 BETA. Length = 367	gnl|PID|e2865 36	99	344	100	100	HKGCW94
76	715445	DNA-PK [Homo sapiens] >pir|G02083|G02083 DNA-PK - human (fragment) >sp|Q13337|Q13337 DNA-PK (FRAGMENT). Length = 930	gi|1017757	119	988	99	99	HLTDJ07
77	716362			221	688			HBGBC77

78	716835	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi|3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp|O14745|O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi|2920585	3	755	79	79	HCHAI81
79	716947	SRp55-2 [Homo sapiens] Length = 135	gi|1049084	2	145	100	100	HADDY71
80	717685	alpha-mannosidase [Homo sapiens] Length = 987	gi|1419374	2	1120	99	99	HDPUO15
81	719755			89	802			HCGAC54
82	720389	inducible membrane protein [Homo sapiens] >gi|806806 cell surface glycoprotein [Homo sapiens] >gi|1832296 metastasis suppressor [Homo sapiens] >pir|I38942|A46493 metastasis suppressor KAI1 - human >sp|P27701|CD82_HUMAN CD82 ANTIGEN (INDUCIBLE MEMBRANE PRO	gi|35833	1	594	65	67	HUVCR41
83	720903	cDNA isolated for this protein using a monoclonal antibody directed against the p27k prosomal protein [Homo sapiens] Length = 266	gnl|PID|e1031 61	108	614	93	95	HFVIH35

84	721348	G6PD (AA 1-515) [Homo sapiens] >sp|P11413|G6PD_HUMAN GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (EC 1.1.1.49) (G6PD). {SUB 2-515} >gi|439445 glucose-6-phosphate dehydrogenase [Didelphis virginiana] {SUB 258-288} >sp|O46666|O46666 GLUCOSE-6-PHOSPHATE DEHYDROGENAS	gi|31543	545	2065	93	93	HSHBL14
85	721562	pescadillo [Homo sapiens] >sp|O00541|O00541 PESCADILLO. Length = 588	gi|2194203	32	811	99	99	HCFCK84
86	722775			409	1680			HCHAD52
87	724463			126	335			HOFMP50
88	727501	SWI/SNF complex 170 KDa subunit [Homo sapiens] >sp|Q92923|Q92923 SWI/SNF COMPLEX 170 KDA SUBUNIT. Length = 1213	gi|1549241	1	1302	97	97	HLYBV46
89	728418	GTP binding protein [Mus musculus] >pir|A39611|A39611 probable GTP-binding protein - mouse >sp|P23249|MV10_MOUSE PROTEIN MOV-10. >gi|433685 gb 110 /Mov 10 locus gene product [Mus musculus] {SUB 1-45} Length = 1004	gi|53169	3	911	93	96	HSSEP09
90	728920	adipophilin [Homo sapiens] >sp|Q99541|Q99541 ADIPOPHILIN (FRAGMENT). Length = 437	gnl|PID|e292752	2	751	89	89	HLDRQ71
91	732958			3	296			HPTYA52

92	733134	NF45 protein [Homo sapiens] >pir|A54857|A54857 transcription factor NF-AT 45K chain - human >sp|Q12905|Q12905 NF45 PROTEIN. Length = 406	gi|532313	84	1259	100	100	HHBHP80
93	734099			150	365			HBGDI44
94	734599			163	705			H6EED05
95	736019	ribosomal protein L11 [Homo sapiens] >gi|57678 ribosomal protein L11 [Rattus rattus] >pir|S17351|R5RT11 ribosomal protein L11 precursor - rat >sp|G3115334|G3115334 RIBOSOMAL PROTEIN L11. >sp|D1026769|D1026769 RIBOSOMAL PROTEIN L11 (FRAGMENT). {SUB 17-52}	gi|3115334	3	608	100	100	HSEBB02
96	738268			45	233			HE2OC41
97	738911	(AF069291) hT41 [Homo sapiens] >sp|G3687829|G3687829 HT41. Length = 505	gi|3687829	3	656	40	62	HCHCI12
98	739226			3	125			HADFY59
99	739527			3	752			HACCL62
100	740710	acyl-CoA synthetase-like protein [Homo sapiens] Length = 670	gnl|PID|e3212 96	8	307	96	100	HPMFQ72

101	742980	serine-threonine specific protein phosphatase [Homo sapiens] >sp|E1334695|E1334695 SERINE-THREONINE SPECIFIC PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 317	gnl|PID|e1334695	3	182	81	86	HSKCE51
102	744331	ZINC FINGER PROTEIN {N-TERMINAL}. Length = 77	sp|G632682|G632682	432	791	62	80	HCHAH75
103	744751	collagen alpha 3(VI) chain precursor - human Length = 2970	pir|S13679|CGHU3A	902	1189	100	100	HUFFV63
104	745750			349	714			HCEHX66
105	746285			2016	2297			HNTNQ78
106	746416	(AB013357) 49 kDa zinc finger protein [Mus musculus] Length = 460	gnl|PID|d1038083	113	391	97	97	HOFMO90
107	747851	(AF035387) C7-1 protein [Rattus norvegicus] >sp|O54715|O54715 C7-1 PROTEIN. Length = 463	gi|2655418	3	974	78	80	HSSJG21
108	750632			252	449			HOGBF68
109	751315			423	608			HLTGN10
110	754009			408	773			HE8PN81
111	754634			525	1070			HUSGH70
112	756637	(AF044127) peroxisomal short-chain alcohol dehydrogenase [Homo sapiens] >sp|G4105190|G4105190 PEROXISOMAL SHORT-CHAIN ALCOHOL DEHYDROGENASE. Length = 260	gi|4105190	38	586	89	91	HMWIY27

113	756833			1	387			HCEDP17
114	756878			127	399			HHBDE92
115	757332	cytokeratin 8 [Homo sapiens] >gi|553163 keratin 8 [Homo sapiens] {SUB 1-231} Length = 482	gi|181573	35	235	96	100	HOFMI52
116	760835	Pectinase gene transcriptional regulator. [Escherichia coli] >gnl|PID|d1015936 Pectinase gene transcriptional regulator. [Escherichia coli] >gi|1787806 (AE000250) putative transcriptional regulator LYSR-type [Escherichia coli] >pir|A64907|A64907 hypotheti	gnl|PID|d1015928	3	434	100	100	HE9BW44
117	761760	F45G2.10 [Caenorhabditis elegans] >sp|O62252|O62252 F45G2.10 PROTEIN. Length = 160	gnl|PID|e1346724	3	527	61	81	HMWIF41
118	762520	B-myb protein (AA 1-700) [Homo sapiens] >pir|S01991|S01991 transforming protein B-myb - human >sp|P10244|MYBB_HUMAN MYB-RELATED PROTEIN B (B-MYB). Length = 700	gi|29472	77	520	100	100	HBJJB76
119	764461			2	211			HOFMH95
120	764517	phosphomevalonate kinase [Homo sapiens] >sp|Q15126|PMKA_HUMAN PHOSPHOMEVALONATE KINASE (EC 2.7.4.2) (PMKASE). {SUB 2-192} >gi|3445542 (AF026069) phosphomevalonate kinase [Homo sapiens] {SUB 33-192} Length = 192	gi|1294782	260	877	100	100	HCGAA73

121	765132	clk1; putative [Homo sapiens] >pir|S53641|S53641 protein kinase clk1 (EC 2.7.1.-) - human >sp|P49759|CLK1_HUMAN PROTEIN KINASE CLK1 (EC 2.7.1.-) (CLK). Length = 484	gi|632964	1202	2251	99	99	HE9QA05
122	765667	(AF043250) mitochondrial outer membrane protein [Homo sapiens] >gi|3941347 (AF043253) mitochondrial outer membrane protein [Homo sapiens] >gi|4105703 (AF050154) D19S1177E [Homo sapiens] >sp|G3941342|G3941342 MITOCHONDRIAL OUTER MEMBRANE PROTEIN. >sp|G3941	gi|3941342	144	1115	91	91	HCHOB54
123	767113	putative progesterone binding protein [Homo sapiens] >sp|O00264|O00264 PUTATIVE PROGESTERONE BINDING PROTEIN. Length = 195	gnl|PID|e3141 74	66	677	93	93	HNTMW26
124	767204	cytochrome P450IIC4 [Oryctolagus cuniculus] >pir|S20227|S20227 cytochrome P450 2C4 - rabbit (fragment) >sp|Q29507|Q29507 CYTOCHROME P450 (EC 1.14.14.1) (FRAGMENT). Length = 145	gi|164933	3	581	43	61	HCHAN75
125	767400			2	1057			HSYBI74

126	767962	proteasome subunit C3 [Homo sapiens] >pir|S15970|SNHUC3 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C3 - human >sp|P25787|PRC3_HUMAN PROTEASOME COMPONENT C3 (EC 3.4.99.46) (MACROPAIN SUBUNIT C3) (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT	gnl|PID|d1001115	3	722	100	100	HABAF63
127	768040	(AB002086) p47 [Rattus norvegicus] >gnl|PID|e294068 XY40 protein [Rattus norvegicus] >sp|O35987|O35987 P47, COMPLETE CDS. Length = 370	gnl|PID|d1022509	119	661	84	89	HSRDI53
128	769956	adenine phosphoribosyltransferase [Homo sapiens] >gi|28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir|S06232|RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp|P07741|APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)	gi|178867	2	592	100	100	HUFFC71
129	770133			958	1236			HUSAX93
130	770289	ALDH7 [Homo sapiens] >pir|I38669|I38669 ALDH7 - human >sp|P43353|DHA7_HUMAN ALDEHYDE DEHYDROGENASE 7 (EC 1.2.1.5). >sp|G601780|G601780 ALDH7. Length = 468	gi|601780	194	340	65	69	HCHAO38

131	771964	(AD000092) human RAD23A homolog [Homo sapiens] >gnl|PID|d1005299 HHR23A protein [Homo sapiens] >pir|S44443|S44443 RAD23 protein homolog2 - human Length = 363	gi|1905912	29	1165	76	76	HAMGD77
132	772582	B-myb protein (AA 1-700) [Homo sapiens] >pir|S01991|S01991 transforming protein B-myb - human >sp|P10244|MYBB_HUMAN MYB-RELATED PROTEIN B (B-MYB). Length = 700	gi|29472	150	974	99	99	HYAAO51
133	773387	zinc finger protein [Homo sapiens] >pir|I38620|I38620 zinc finger protein ZNF155 - human (fragment) Length = 139	gi|495576	152	634	46	64	HAJBC78
134	773827	novel serine protease, PRSS11 [Homo sapiens] >gnl|PID|d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp|Q92743|Q92743 NOVEL SERINE PROTEASE. Length = 480	gnl|PID|e275186	3	1217	100	100	HKADF15
135	774108	protein of unknown function [Homo sapiens] >pir|C35826|C35826 hypothetical protein A, 13K - human >sp|Q00994|HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gi|189379	303	623	75	75	HEGAC01

136	774636	glutathione transferase [Homo sapiens] >pir|A39375|A39375 glutathione transferase (EC 2.5.1.18) class mu, GSTM2 - human >sp|P28161|GTM2_HUMAN GLUTATHIONE S-TRANSFERASE MU 2 (EC 2.5.1.18) (GSTM2-2) (CLASS-MU). {SUB 2-218} >gnl|PID|e33921 glutathione transf	gi|183301	61	747	98	98	HISDV78
137	775339	SWI/SNF complex 60 KDa subunit [Homo sapiens] >sp|Q92924|Q92924 SWI/SNF COMPLEX 60 KDA SUBUNIT. Length = 435	gi|1549243	3	320	98	100	HSIGB35
138	775582			448	705			HEPNB30
139	775779	(AJ000332) Glucosidase II [Homo sapiens] >sp|Q14697|Q14697 GLUCOSIDASE II PRECURSOR (KIAA0088). >gnl|PID|d1008224 The ha1225 gene product is related to human alpha-glucosidase. [Homo sapiens] {SUB 2-944} Length = 944	gnl|PID|e328143	1	1695	98	98	HLWAS86
140	777809	cysteine-rich protein 2 [Homo sapiens] >gnl|PID|d1008288 ESP1/CRP2 [Homo sapiens] >pir|G02090|G02090 cysteine-rich protein 2 - human >sp|P52943|CRP2_HUMAN CYSTEINE-RICH PROTEIN 2 (CRP2) (ESP1 PROTEIN). Length = 208	gi|1399028	202	681	99	100	HSPMB57
141	778927	valyl-tRNA synthetase [Homo sapiens] >pir|S17675|S17675 valine--tRNA ligase (EC 6.1.1.9) - human Length = 1265	gi|31545	1843	3282	88	88	HMVBW39

142	779262			1	288			HTENK29
143	779392			2	181			HE2FO87
144	780149	proteasome activator hPA28 suunit beta [Homo sapiens] >pir|I53518|I53518 proteasome activator hPA28 suunit beta - human >sp|Q15129|Q15129 PROTEASOME ACTIVATOR HPA28 SUUNIT BETA. >sp|G693763|G693763 PA28=REGULATORS OF THE 20 S PROTEASOME {PEPTIDE 15}. {SUB	gnl|PID|d1008800	233	955	93	93	HSPMF83
145	780583			8	607			HHEOW04
146	780960			232	576			HOEBN65
147	781469	radixin [Homo sapiens] >pir|A46127|A46127 radixin - human Length = 583	gi|307366	1	303	100	100	HNTRA25
148	781556			116	190			HOSAW82
149	781771			1	822			HE6EO05
150	782033	histone H2A [Gallus gallus] Length = 129	gi|1493827	146	544	98	100	HULCC66
151	782105			606	1064			HKAKV16

152	782122	high density lipoprotein binding protein [Homo sapiens] >pir|A44125|A44125 high density lipoprotein-binding protein, 110K - human >sp|Q00341|HBP_HUMAN HIGH DENSITY LIPOPROTEIN BINDING PROTEIN (HDL-BINDING PROTEIN). >sp|G1478463|G1478463 VIGILIN=KH PROTEIN	gi|183892	3	983	95	95	HSRAB32
153	783135	zinc finger protein [Homo sapiens] >sp|O00488|O00488 ZINC FINGER PROTEIN. Length = 116	gnl|PID|d1021201	3	500	97	99	HCHCB61
154	783245			3	341			HTSFV77
155	783247			95	391			HBGMD18
156	783413	D9 splice variant 3 [Mus musculus] >sp|O08695|O08695 D9 SPLICE VARIANT 3. Length = 169	gi|2071991	1	591	80	88	HEBFR23
157	784407			45	185			HFKAA09
158	784548	nuclear RNA helicase (DEAD family) [Homo sapiens] >pir|I37201|I37201 nuclear RNA helicase (DEAD family) BAT1 - human >sp|Q13838|HE47_HUMAN PROBABLE ATP-DEPENDENT RNA HELICASE P47. >gi|2739119 (AF029061) BAT1 [Homo sapiens] {SUB 145-428} >gi|971677 express	gi|587146	676	1020	90	92	HSRFZ85

159	785075	KIAA0100 is a human counterpart of mouse e1 gene. [Homo sapiens] >sp|Q14667|Q14667 KIAA0100 (HUMAN COUNTERPART OF MOUSE E1 GENE). Length = 2092	gnl|PID|d1008477	72	1109	93	93	HDPFX40
160	785677	(AC004084) similar to DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE; 98% similar to P5243 (PID:g1710661) [Homo sapiens] >sp|O43375|O43375 SIMILAR TO DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE (FRAGMENT). Length = 105	gi|2822158	1	273	95	100	HBSAJ50
161	786238			2	994			HOVCA75
162	786389			3	1124			HLJDU61
163	786929	(AJ224442) methyltransferase [Homo sapiens] >sp|O43709|O43709 METHYLTRANSFERASE. Length = 220	gnl|PID|e1253426	123	404	86	95	HOFNV27
164	786932	PIPPin protein [Rattus norvegicus] >pir|JC4588|JC4588 RNA-binding protein PIPPin - rat >sp|Q63430|Q63430 PIPPIN PROTEIN. Length = 154	gi|1050754	2	490	76	87	HUSYH27
165	787078	HER2 receptor [Homo sapiens] >gi|553282 c-erb-2 protein [Homo sapiens] {SUB 737-1031} >gi|553332 HER-2/neu [Homo sapiens] {SUB 1-191} >gi|183989 HER2 receptor (AA at 3) [Homo sapiens] {SUB 740-910} >gi|182169 c-erb B2/neu protein [Homo sapiens] {SUB 1081-	gi|306840	236	1114	79	79	HCHND12

166	787139			230	625			HBCBA06
167	787283			3	656			HFOYO96
168	788761	MAL3P6.24 [Plasmodium falciparum] >sp|O77371|O77371 MAL3P6.24 PROTEIN. Length = 1017	gnl|PID|e1331909	2	700	36	60	HTXFK57
169	788988	(AF023611) Dim1p homolog [Homo sapiens] >sp|O14834|O14834 DIM1P HOMOLOG. Length = 142	gi|2565275	70	417	98	98	HUSGH90
170	789092			2	400			H6EBE80
171	789298	(AF044311) gamma-synuclein [Homo sapiens] >gi|3642775 (AF017256) persyn [Homo sapiens] >gi|3642903 (AF037207) persyn [Homo sapiens] >sp|O76070|O76070 PERSYN. Length = 127	gi|3347842	1	489	82	82	HTSFM20
172	789299			205	381			HBGDD91
173	789718			233	580			HBGBT30
174	789957	beta-hexosaminidase alpha chain [Homo sapiens] >pir|A23561|AOHUBA beta-N-acetylhexosaminidase (EC 3.2.1.52) alpha chain precursor - human >sp|P06865|HEXA_HUMAN BETA-HEXOSAMINIDASE ALPHA CHAIN PRECURSOR (EC 3.2.1.52) (N-ACETYL-BETA-GLUCOSAMINIDASE) (BETA-	gi|179458	750	1619	99	99	HISEM44

175	789977	arginyl-tRNA synthetase, ArgRS [human, ataxia-telangiectasia patients, EBV-lymphoblastoid cells, Peptide, 659 aa] [Homo sapiens] >pir|JC4365|JC4365 arginine--tRNA ligase (EC 6.1.1.19) - human Length = 659	bbs|173838	25	2019	94	95	HMEIU30
176	790285	HCG V [Homo sapiens] >sp|O60927|O60927 HCG V. Length = 126	gi|3176438	44	391	85	85	HDPCH88
177	790509	human elongation factor-1-delta [Homo sapiens] >pir|S34626|S34626 translation elongation factor eEF-1 delta chain - human >sp|P29692|EF1D_HUMAN ELONGATION FACTOR 1-DELTA (EF-1-DELTA). Length = 281	gi|38522	227	1108	63	64	HPMGB64
178	790775			950	1351			HJAAO21
179	790888	(AF036956) neuroblastoma apoptosis-related RNA binding protein [Homo sapiens] >sp|G4104559|G4104559 NEUROBLASTOMA APOPTOSIS-RELATED RNA BINDING PROTEIN. Length = 490	gi|4104559	2	274	100	100	HE8QE19
180	791506			2	205			HOFMB93
181	791649			3	359			HBGBH10
182	791802			165	695			HWLRH03

183	792002	ADP-ribosylation factor [Homo sapiens] >gi|2088529 ADP-ribosylation factor 5 [Homo sapiens] >gi|438870 ADP-ribosylation factor 5 [Rattus norvegicus] >gnl|PID|d1014187 ARF5 [Mus musculus] >pir|A23741|A23741 ADP-ribosylation factor 5 - human >pir|JC4949|JC4	gi|178987	2	655	100	100	HHENT53
184	792291	see GenBank Accession Number U01184 for cDNA; similar to Drosophila melanogaster flil in GenBank Accession Number U01182 and Caenorhabditis elegans flil homolog in GenBank Accession Number U01183 [Homo sapiens] >sp|Q13045|Q13045 FLIGHTLESS-I PROTEIN HOMOL	gi|2138290	843	3329	96	96	HDPIT69
185	792371			3	665			HUSJW77
186	792660	(AF044773) breakpoint cluster region protein 1 [Homo sapiens] >sp|O60558|O60558 BREAKPOINT CLUSTER REGION PROTEIN 1. Length = 138	gi|3002951	116	406	100	100	HCHMC26
187	792782			41	838			HTXJB38
188	792890	(AF001846) lymphoid phosphatase LyP1 [Homo sapiens] >sp|G4100632|G4100632 LYMPHOID PHOSPHATASE LYP1. Length = 808	gi|4100632	2	994	90	90	HHESJ29
189	792931			1	576			HEGAW71

190	792943	myosin heavy chain kinase B [Dictyostelium discoideum] >sp|P90648|KMHB_DICDI MYOSIN HEAVY CHAIN KINASE B (EC 2.7.1.129) (MHCK B). Length = 732	gi|1903458	3	1247	43	68	HDPRZ79
191	793104			107	250			HKGAJ80
192	793445	desmoyokin - human (fragments) >sp|Q09666|AHNK_HUMAN NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN AHNAK (DESMOYOKIN) (FRAGMENTS). >gi|178281 AHNAK nucleoprotein [Homo sapiens] {SUB 1-1683} >gi|897824 AHNAK gene product [Homo sapiens] {SUB 1684-2960} Leng	pir|A45259|A45259	1	723	92	92	HDTEJ86
193	793446			25	255			HHBGY94
194	793639	(AF044959) NADH:ubiquinone oxidoreductase NDUFS6 subunit [Homo sapiens] >sp|O75380|NUMM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE 13 KD-A SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-13KD-A) (CI-13KD-A). Length = 124	gi|3348137	1	411	100	100	HLJBJ72
195	794213	100 kDa protein [Rattus norvegicus] >pir|S22659|S22659 hypothetical protein, 100K - rat >sp|Q62671|100K_RAT 100 KD PROTEIN (EC 6.3.2.-). Length = 889	gi|55535	326	691	93	95	HLWCN67
196	795858			1020	1205			HLYDY53

197	795955	c-myc binding protein [Homo sapiens] >sp|Q99471|MM1_HUMAN C-MYC BINDING PROTEIN MM-1. >sp|D1014706|D1014706 C-MYC BINDING PROTEIN. Length = 167	gnl|PID|d1014706	31	507	100	100	HUSXX36
198	796359	ribosomal protein L7a large subunit [Homo sapiens] >gi|34203 L7a protein [Homo sapiens] >gi|35512 PLA-X polypeptide [Homo sapiens] >gi|36647 ribosomal protein L7a [Homo sapiens] >gi|56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir|S19717|R5HU7A	gi|337495	19	297	100	100	HOFNW79
199	796555	DJ366N23.3 (KIAA0173 AND TUBULIN-TYROSINE LIGASE LIKE) (FRAGMENT). Length = 278	sp|O75653|O75653	1	1086	44	62	HLWEW04
200	796675	PEG1/MEST [Homo sapiens] >sp|O15007|O15007 PEG1/MEST GENE MRNA. Length = 335	gnl|PID|e307037	44	1027	100	100	HSICR25
201	796743	(AF022229) translation initiation factor 6 [Homo sapiens] >gnl|PID|e304603 b4 integrin interactor [Homo sapiens] >gi|3335506 (AF047433) b(2)gcn homolog [Homo sapiens] >sp|P56537|IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT	gi|2809383	30	842	100	100	H6EDU12
202	796792			198	461			HDTII72
203	799668			166	303			HODBC01
204	799669			2	310			HOGAV29

205	799673			2	310			HOFMN53
206	799674			130	1044			HCHMI60
207	799678	ribosomal protein L18a [Homo sapiens] >gi|3702270 (AC005796) ribosomal protein L18a [Homo sapiens] >gnl|PID|d1029536 (AB007175) ribosomal protein L18a [Homo sapiens] {SUB 111-176} Length = 176	gi|401845	40	345	98	98	HOFNL25
208	799728			3	179			HBGBG75
209	799748			1	660			HCHMQ24
210	799760	o361 [Escherichia coli] >gi|1790125 (AE000446) orf, hypothetical protein [Escherichia coli] >pir|C65171|C65171 hypothetical 41.0 kD protein in ibpA-gyrB intergenic region - Escherichia coli (strain K-12) Length = 361	gi|290539	1	357	99	100	HBGBF66
211	799805			2	118			HBGDA22
212	800296	CDC37 homolog [Homo sapiens] >gi|1375485 CDC37 homolog [Homo sapiens] >pir|G02313|G02313 CDC37 homolog - human >sp|Q16543|Q16543 CDC37 HOMOLOG. Length = 378	gi|1421821	2	802	89	89	HDABE68

213	800327	ADP-ribosylation factor-like protein 2 [Homo sapiens] >pir|A48259|A48259 ADP-ribosylation factor-like 2 - human >sp|P36404|ARL2_HUMAN ADP-RIBOSYLATION FACTOR-LIKE PROTEIN 2. >sp|G425655|G425655 ARL2=ADP-RIBOSYLATION FACTOR HOMOLOG. Length = 184	gi|3009501	25	645	99	99	HCHPG41
214	800816			115	351			HODCV09
215	800835	(AF071538) Ets transcription factor PDEF [Homo sapiens] >sp|G4007418|G4007418 ETS TRANSCRIPTION FACTOR PDEF. Length = 335	gi|4007418	3	881	96	96	HETJP29
216	805429	RanGAP1 [Homo sapiens] >pir|JC5300|JC5300 Ran GTPase activator 1 - human Length = 587	gi|575268	3	683	90	90	HKABS06
217	805458	(AF044221) HCG-1 protein [Homo sapiens] >sp|G4105252|G4105252 HCG-1 PROTEIN. Length = 117	gi|4105252	745	1122	100	100	HDQEV55
218	805478			60	644			HDQGR35
219	805805	19 kDa subunit of NADH:ubiquinone oxidoreductase complex (complex I) [Bos taurus] >pir|S16208|S16208 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 19K chain - bovine >sp|P42029|NUPM_BOVIN NADH-UBIQUINONE OXIDOREDUCTASE 19 KD SUBUNIT (EC 1.6.5.3) (EC 1.6.99	gi|599681	2	478	87	90	HOFMH12
220	806486			3	62			HFXJC33

221	806498			518	1741			HIBCA25
222	806819	acidic ribosomal phosphoprotein (P0) [Homo sapiens] >gi|2935618 (AC004263) 60S ACIDIC RIBOSOMAL PROTEIN; match to P05388 (PID:g133041) [Homo sapiens] >pir|A27125|R5HUP0 acidic ribosomal protein P0 - human >sp|D1026785|D1026785 RIBOSOMAL PROTEIN P0 (FRAGME	gi|190232	3	866	81	84	HOFAC09
223	810870	thrombospondin-4 [Homo sapiens] >pir|A55710|TSHUP4 thrombospondin 4 precursor - human Length = 961	gi|311626	2	1333	99	99	HBOEB83
224	811730			2	979			HCHPJ26
225	813025	heat shock protein 86 [Homo sapiens] >sp|Q14568|Q14568 HEAT SHOCK PROTEIN 86 (FRAGMENT). Length = 312	gi|292162	106	492	88	89	HOFMD78
226	813233	co-beta glucosidase precursor [Homo sapiens] >gi|337762 prosaposin [Homo sapiens] >gi|337756 sphingolipid activator precursor [Homo sapiens] Length = 524	gi|183231	1	468	81	90	HOFMF17
227	813262			1	345			HFKCA89
228	815637	(AC004003) serine/threonine kinase RICK; match to protein AF027706 (PID:g3123887) and mRNA AF027706 (NID:g3123886) [Homo sapiens] >gi|3290172 (AF064824) CARD-containing ICE associated kinase [Homo sapiens] >gi|3342910 (AF078530) receptor	gi|3264574	3	461	92	92	HNHDS66

		interacting prote						
229	815853	calcyphosine [Homo sapiens] >gi|3075376 (AC004602) CAYP_HUMAN; RD25 [Homo sapiens] >sp|Q13938|CAYP_HUMAN CALCYPHOSINE. Length = 189	gnl|PID|e245872	8	667	100	100	HLHAY85
230	815999	S100 calcium-binding protein A13 (S100A13) [Homo sapiens] >pir|JC5064|JC5064 S-100 calcium-binding protein A13 - human Length = 98	gnl|PID|e268253	68	421	42	70	HKABX07
231	823427			1	927			HTLGL50
232	823704	(AC004770) BC269730_2 [Homo sapiens] >sp|O60427|O60427 BC269730_2. Length = 444	gi|3169158	3	860	67	80	HDABC49
233	824798			307	858			HDQGK75
234	825018			2	1924			HETIS29
235	825076	Whole ORF continues from bp19 (right after 'tag') to bp1596 ('tga').; similar to chinese hamster phosphatidylserine synthase. [Homo sapiens] Length = 473	gnl|PID|d1004031	2	1549	92	92	HE9PJ48

236	825787	EXT2 [Homo sapiens] >gi|1621113 hereditary multiple exostoses gene 2 protein [Homo sapiens] >gi|1519605 multiple exostosis 2 [Homo sapiens] >sp|Q93063|EXT2_HUMAN EXOSTOSIN-2 (PUTATIVE TUMOUR SUPPRESSOR PROTEIN EXT2) (MULTIPLE EXOSTOSES PROTEIN 2). Length	gi|1518042	305	2293	100	100	HEONV84
237	826116	BETA CRYSTALLIN S (GAMMA CRYSTALLIN S). >gi|557548 crystallin [Homo sapiens] {SUB 19-106} Length = 177	sp|P22914|CRBS_HUMAN	392	682	86	87	HAJAE27
238	826147	neural specific protein CRMP-2 [Bos taurus] >sp|O02675|DPY2_BOVIN DIHYDROPYRIMIDINASE RELATED PROTEIN-2 (DRP-2) (NEURAL SPECIFIC PROTEIN NSP60). Length = 572	gi|1916227	3	503	98	98	HCEPT06
239	827020	(AF027954) Bcl-2-related ovarian killer protein [Rattus norvegicus] >gi|2689660 (AF027707) apoptosis activator Mtd [Mus musculus] >sp|O35425|O35425 BCL-2-RELATED OVARIAN KILLER PROTEIN. Length = 213	gi|2645560	12	539	95	97	HHFHE17
240	827586	calmodulin [Plasmodium falciparum] >gi|160128 calmodulin [Plasmodium falciparum] >pir|B45594|MCZQF calmodulin - Plasmodium falciparum >sp|P24044|CALM_PLAFA CALMODULIN. Length = 149	gi|385234	85	495	49	76	HCHMW40

241	827732	alternate name ygiG; ORF_f123 [Escherichia coli] >gi|1789438 (AE000387) putative kinase [Escherichia coli] >pir|H65093|H65093 ygiG protein - Escherichia coli (strain K-12) >sp|P31055|FOLB_ECOLI PROBABLE DIHYDRONEOPTERIN ALDOLASE (EC 4.1.2.25) (DHNA). {SUB	gi|882580	181	282	91	95	HBGDE81
242	827735			541	708			HHEDU22
243	827740			716	838			HBNAP17
244	827808			86	1657			HMELR44
245	828251	(AB016869) p70 ribosomal S6 kinase beta [Homo sapiens] >sp|D1035383|D1035383 P70 RIBOSOMAL S6 KINASE BETA. Length = 495	gnl|PID|d103 5383	134	949	91	91	HNGOL64
246	828357			1	768			HKIYP61
247	828449			1	723			HBXCZ22
248	828612	syntaxin 5 [Homo sapiens] >pir|G01817|G01817 syntaxin 5 - human Length = 301	gi|886071	68	460	100	100	HNHMY58
249	828647	laminin beta 2 chain [Homo sapiens] >sp|P55268|LMB2_HUMAN LAMININ BETA-2 CHAIN PRECURSOR (S-LAMININ). Length = 1798	gnl|PID|e2132 86	299	2254	85	85	HRABB47

250	828698	galactokinase [Homo sapiens] >gi|1929895 galactokinase [Homo sapiens] >sp|P51570|GALI_HUMAN GALACTOKINASE I (EC 2.7.1.6). >gi|3603423 (AF084935) galactokinase [Homo sapiens] {SUB 1-264} Length = 392	gi|1002507	3	1220	83	83	HKGAU37
251	828962	secretory protein [Homo sapiens] >gi|940946 intestinal trefoil factor [Homo sapiens] >pir|A48284|A48284 intestinal trefoil factor 3 precursor - human >sp|Q07654|ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HP1.B). Length = 80	gi|402483	2	259	78	78	HCHMR52
252	828982	unnamed protein product [unidentified] >gi|189500 p62 [Homo sapiens] >pir|A38219|A38219 GAP-associated tyrosine phosphoprotein p62 - human >sp|Q07666|Q07666 GAP-ASSOCIATED TYROSINE PHOSPHOPROTEIN P62. >gnl|PID|e1259626 unnamed protein product [unidentifie	gnl|PID|e1259622	1	1176	85	85	HE9PC52
253	829282			289	828			HCHOB95
254	829368			279	512			HWGAA79
255	829751			2	418			HCHMB33
256	829773	(AF109906) G9A [Mus musculus] >sp|G3986768|G3986768 G9A. Length = 1000	gi|3986768	26	862	97	98	HMWBV67

257	829934	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir|A35954|A35954 endoplasmin precursor - human >sp|P14625|ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803	gi|37261	1142	2356	94	94	HFIIJ68
258	829942	dynamitin [Homo sapiens] >sp|Q13561|DYNC_HUMAN DYNACTIN, 50 KD ISOFORM (50 KD DYNEIN-ASSOCIATED POLYPEPTIDE) (DYNAMITIN). Length = 406	gi|1255188	15	1409	85	85	HUFBF69
259	829951			119	262			HBGBA32
260	830173	death associated protein 5 [Homo sapiens] >sp|O60877|O60877 DEATH ASSOCIATED PROTEIN 5. Length = 907	gnl|PID|e1298888	51	2870	90	90	HETJX39
261	830200			3	638			HBGMF83
262	830365	mevalonate pyrophosphate decarboxylase [Homo sapiens] >sp|P53602|ER19_HUMAN DIPHOSPHOMEVALONATE DECARBOXYLASE (EC 4.1.1.33) (MEVALONATE PYROPHOSPHATE DECARBOXYLASE). Length = 400	gi|1235682	56	1291	95	95	HUSJG21
263	830456			215	397			HCFBN01

264	830549	guanine nucleotide-binding regulatory protein-beta-2 subunit [Homo sapiens] >gi|339935 transducin beta-2 subunit [Homo sapiens] >gi|3135310 (AF053356) GNB2 [Homo sapiens] >pir|B26617|RGHUB2 GTP-binding regulatory protein beta-2 chain - human >sp|P11016|GB	gi|386751	1	729	100	100	HDPXM12
265	830602			24	461			HTLDJ82
266	830610	zyxin [Homo sapiens] >gnl|PID|e223417 zyxin [Homo sapiens] >pir|G02845|G02845 zyxin - human Length = 572	gnl|PID|e218260	956	1855	94	94	HDPRN35
267	830644	(AF104260) hiwi [Homo sapiens] >sp|G4038413|G4038413 HIWI (FRAGMENT). Length = 523	gi|4038413	2	391	99	99	HTEEU95
268	830707			3	623			HETCJ14
269	830709			2	304			HSSGN20
270	830733			540	725			HSNAD86
271	830768	carboxylesterase hCE-2 [Homo sapiens] >sp|Q16859|Q16859 CARBOXYLESTERASE (EC 3.1.1.1) (ALI-ESTERASE) (B-ESTERASE) (MONOBUTYRASE) (COCAINE ESTERASE) (PROCAINE ESTERASE) (METHYLBUTYRASE). Length = 550	gi|1407780	623	2269	99	99	HDPFX44
272	830855			1	465			HJPCE06

273	830949			2457	2903			HCE5J35
274	830965			139	792			HOHCA01
275	830973			354	557			HRODL42
276	830979	THIOREDOXIN REDUCTASE 2. Length = 526	sp|G3757888|G3757888	753	1454	81	90	HOGCC93
277	830989	La protein [Homo sapiens] >gi|36415 ribonucleoprotein SS-B/La (AA 1-408) [Homo sapiens] >pir|A31888|A31888 ribonucleoprotein La - human >sp|P05455|LA_HUMAN LUPUS LA PROTEIN (SJOGREN SYNDROME TYPE B ANTIGEN (SS-B)) (LA RIBONUCLEOPROTEIN) (LA AUTOANTIGEN).	gi|178687	3	1382	87	87	HDQFZ49
278	831134			2	241			HBXEB46
279	831200			3	773			HADXB20
280	831260			892	1095			HLWBR58
281	831531	transcription factor [Homo sapiens] >gi|37058 IIB protein [Homo sapiens] >pir|S17654|TWHU2B transcription initiation factor IIB - human >bbs|112738 S300-II, TFIIB=transcription factor [human, Peptide Partial, 311 aa] [Homo sapiens] {SUB 6-316} Length = 31	gi|339490	93	1172	95	95	HHPGX85
282	831665			2	1093			HSKDH81

283	831724			1	468			HFEBQ94
284	831884	(AF034800) liprin-alpha3 [Homo sapiens] >sp|G3309535|G3309535 LIPRIN-ALPHA3 (FRAGMENT). Length = 443	gi|3309535	20	469	90	90	HDTGO74
285	831897	laminin B1 [Homo sapiens] >gi|186876 laminin B1 [Homo sapiens] >gi|186913 laminin B1 [Homo sapiens] >pir|S13547|MMHUB1 laminin chain B1 precursor - human >sp|P07942|LMB1_HUMAN LAMININ BETA-1 CHAIN PRECURSOR (LAMININ B1 CHAIN). Length = 1786	gi|186837	1	1581	92	92	HSKHV84
286	831922			499	684			HDQIB68
287	831963			188	319			HDPGS84
288	832074	gluconate kinase [Escherichia coli] >gi|1790719 (AE000497) gluconate kinase, thermosensitive glucokinase [Escherichia coli] >pir|S56494|S56494 gluconokinase (EC 2.7.1.12) gntV - Escherichia coli >sp|P39208|GNTV_ECOLI THERMOSENSITIVE GLUCONOKINASE (EC 2.7.	gi|537110	1	579	42	58	HCRNT71
289	832266			71	433			HNGJU70
290	832309			1891	2226			HBJDT21
291	832342	fatty acid amide hydrolase [Homo sapiens] >sp|O00519|O00519 FATTY ACID AMIDE HYDROLASE. Length = 579	gi|2149156	9	224	97	100	HBGDP82

292	832351	unknown product specific to adipose tissue [Homo sapiens] >sp|Q15847|Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl|PID|d1008821	47	298	68	68	HFABE30
293	832352	unknown product specific to adipose tissue [Homo sapiens] >sp|Q15847|Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl|PID|d1008821	89	277	92	94	HOEKX93
294	832434	Cks1 protein homologue [Homo sapiens] >pir|A36670|A36670 protein kinase cdc2 complex subunit CKS1 - human >sp|P33551|CKS1_HUMAN CYCLIN-DEPENDENT KINASES REGULATORY SUBUNIT 1 (CKS-1). Length = 79	gi|29977	78	335	100	100	HFNAB43
295	832490	growth arrest and DNA-damage-inducible protein [Homo sapiens] >gi|403128 [Human gadd45 gene, complete cds.], gene product [Homo sapiens] >pir|A39617|A39617 DNA-damage-inducible protein gadd45 - human >sp|P24522|GA45_HUMAN GROWTH ARREST AND DNA-DAMAGE-INDU	gi|182940	220	798	98	100	HKAKL21
296	832573			30	629			HCHOY13
297	832580	pS2 protein [Homo sapiens] >gi|35707 pS2 precursor [Homo sapiens] >gnl|PID|e223341 pS2 [Homo sapiens] >pir|A26667|A26667 pS2 protein precursor - human >gi|182204 estrogen receptor [Homo sapiens] {SUB 2-84} Length = 84	gi|35718	45	362	100	100	H2LAR67

298	833394			274	588			HBGMC47
299	835355	(AF060567) sushi-repeat protein [Homo sapiens] >sp|O60687|O60687 SUSHI-REPEAT PROTEIN. Length = 465	gi|3108089	3	1295	99	100	HUSAU05
300	835497	(AJ006064) coronin-like protein [Rattus norvegicus] >sp|O89046|O89046 CORONIN-LIKE PROTEIN. Length = 484	gnl|PID|e1331790	334	1584	96	99	HLDDS71
301	835728			2	871			HODAK21
302	835978			643	2019			HTLEB03
303	836091	PDC-E2 precursor (AA -54 to 561) [Homo sapiens] >pir|S01783|XXHU dihydrolipoamide S-acetyltransferase (EC 2.3.1.12) precursor - human (fragment) >gi|345030 Human 70kd mitochondrial antigen of PBC [unidentified] {SUB 179-500} >sp|G254062|G254062 PYRUVATE D	gi|35360	546	2114	99	99	H2CBW86
304	836274	Id4 [Homo sapiens] >gnl|PID|e266418 helix-loop-helix protein [Homo sapiens] >gnl|PID|e1359205 (AL022726) dJ625H18.1 (ID4 Helix-loop-helix DNA binding protein) [Homo sapiens] >gnl|PID|e266418 helix-loop-helix protein [Homo sapiens] >pir|G01855|G01855 Id4 -	gi|881546	2	334	98	98	HCLBP52

305	836731	(AF075599) ubiquitin conjugating enzyme 12 [Homo sapiens] >gnl|PID|d1034111 (AB012191) Nedd8-conjugating enzyme hUbc12 [Homo sapiens] >sp|O76069|O76069 UBIQUITIN-CONJUGATING ENZYME E2 (EC 6.3.2.19) (UBIQUITIN-PROTEIN LIGASE) (UBIQUITIN CARRIER PROTEIN). L	gi|3309661	2	571	100	100	HFXAZ01
306	838014	prolyl 4-hydroxylase alpha (II) subunit [Homo sapiens] >sp|O15460|O15460 PROLYL 4-HYDROXYLASE ALPHA (II) SUBUNIT (II). Length = 535	gi|2439985	3	1574	99	99	HTEHY24
307	838874			271	546			HFPEZ63
308	839120	peptide transporter [Homo sapiens] >pir|S13427|A41538 ATP-binding cassette transporter TAP1 - human >gi|34636 ABC-transporter [Homo sapiens] {SUB 61-808} >gi|930122 Y3 gene product [Homo sapiens] {SUB 183-612} Length = 808	gi|36061	100	2169	90	90	HNFDY03
309	839611			548	793			HAMFI54
310	840138	start position 1 [Homo sapiens] >sp|E1335356|E1335356 ASMTL PROTEIN. >gnl|PID|e1335357 start position 2 [Homo sapiens] {SUB 59-629} Length = 629	gnl|PID|e1335356	1	1800	92	93	HFIHW86

311	840616	Homology with Squid retinal-binding protein (PIR Acc. No. A53057) [Caenorhabditis elegans] >sp|Q22467|Q22467 T13H5.2 PROTEIN. Length = 1254	gnl|PID|e1349397	3	1607	73	86	HMSCY51
312	840780	unknown [Saccharomyces cerevisiae] >pir|S58704|S58704 probable membrane protein YIL003w - yeast (Saccharomyces cerevisiae) >gi|558401 incomplete orf, len: 160, CAI: 0.09 similar to MRP_ECOLI P21590 39.9 KD PROTEIN [Saccharomyces cerevisiae] {SUB 1-158} >g	gi|763343	17	880	57	80	H6EDY61
313	840857	(AF071059) zinc finger RNA binding protein [Mus musculus] >sp|O88532|O88532 ZINC FINGER RNA BINDING PROTEIN. Length = 1052	gi|3293537	459	2669	94	94	HLHDQ83
314	840862	cysteine-rich intestinal protein [Homo sapiens] >pir|G02666|G02666 cysteine-rich protein 1 - human Length = 77	gi|1381638	36	353	100	100	HEPAP58
315	840864			407	1096			HTLHY48
316	840936	homologous to Swiss-Prot accession number P16371 [Homo sapiens] >gi|3850562 (AC005944) GRG_HUMAN; ESP1 PROTEIN; AMINO ENHANCER OF SPLIT; AES-1/AES-2; gp130 associated protein GAM [Homo sapiens] >pir|G01236|G01236 enhancer of split m9/m10 (groucho protein)	gi|435425	3	668	79	79	HOENU32

317	840938	carbonyl reductase [Sus scrofa] >pir|JN0703|JN0703 carbonyl reductase (NADPH) (EC 1.1.1.184) - pig >sp|Q29529|CBR2_PIG LUNG CARBONYL REDUCTASE [NADPH] (EC 1.1.1.184) (NADPH-DEPENDENT CARBONYL REDUCTASE) (LCR). Length = 244	gnl|PID|d1004479	2	745	65	76	HMCAI75
318	841884			677	1324			HLQBI45
319	842241	(AJ009698) embigin protein [Rattus norvegicus] >sp|O88775|O88775 EMBIGIN PROTEIN PRECURSOR. Length = 328	gnl|PID|e1312986	2	952	60	75	HOFMD52
320	843712			2	202			HSSGR77
321	844040	ribosomal protein L11 [Caenorhabditis elegans] >pir|S27795|S27795 ribosomal protein L11 homolog - Caenorhabditis elegans Length = 195	gi|156201	75	500	42	64	HPTGB84
322	844336	(AB009462) LDL receptor related protein 105 [Homo sapiens] >sp|O75074|O75074 LDL RECEPTOR RELATED PROTEIN 105. Length = 770	gnl|PID|d1033292	831	2285	68	75	HWMFE21
323	844612	collagen binding protein 2 [Homo sapiens] >pir|I52968|I52968 colligin-2 - human >sp|P50454|CBP2_HUMAN COLLAGEN-BINDING PROTEIN 2 PRECURSOR (COLLIGIN 2). Length = 418	gnl|PID|d1012496	528	1466	96	97	HOFME75
324	844617			556	735			HMVCZ36

325	845251	LIV-1 protein [Homo sapiens] >pir|G02273|G02273 LIV-1 protein - human >sp|Q13433|Q13433 ESTROGEN REGULATED LIV-1 PROTEIN. Length = 752	gi|1256001	23	634	49	67	HBGBB42
326	845764			2	244			HULCF61
327	846187	ATPase alpha subunit (aa 1-1023) [Homo sapiens] >gnl|PID|d1000505 Na,K-ATPase alpha-subunit [Homo sapiens] >pir|A24414|A24414 Na+/K+-exchanging ATPase (EC 3.6.1.37) alpha-1 chain - human >sp|P05023|ATN1_HUMAN SODIUM/POTASSIUM-TRANSPORTING ATPASE ALPHA-1 C	gi|28927	151	2403	92	92	HDPLV27
328	HBGDH47R			167	241			HBGDH47
329	HHENQ86R			2	112			HHENQ86
330	HBGBH23R	(AE000161) bacteriophage lambda endopeptidase homolog [Escherichia coli] >pir|B64788|B64788 bacteriophage lambda endopeptidase homolog (EC 3.4.-.-) - Escherichia coli (strain K-12) >sp|P75719|ENPP_ECOLI PUTATIVE ENDOPEPTIDASE (EC 3.4.-.-). Length = 153	gi|1786769	1	213	92	92	HBGBH23
331	HANGA53R	(AF013214) acidic ribosomal phosphoprotein PO [Bos taurus] Length = 302	gi|2293577	76	402	80	84	HANGA53

332	HBIMC29R	(AF035959) type-2 phosphatidic acid phosphatase-gamma; phosphatidate phosphohydrolase; phospholipid phosphatase [Homo sapiens] >gi|3025880 (AF056083) phosphatidic acid phosphatase type 2 [Homo sapiens] >gi|2911498 (AF047760) phosphatidic acid phosphohydro	gi|3123896	3	317	96	96	HBIMC29
333	HOFAB89R	(AF061340) F1 ATPase subunit 6 [Artibeus jamaicensis] Length = 226	gi|4164480	86	268	67	82	HOFAB89
334	HAHCP93R	(AF070447) barrier-to-autointegration factor [Homo sapiens] >sp|O75531|O75531 BARRIER-TO-AUTOINTEGRATION FACTOR. Length = 89	gi|3220255	116	289	69	76	HAHCP93
335	HBGAA76R			14	232			HBGAA76
336	HBGBT12R	A (DNA packaging;641) [Bacteriophage lambda] >pir|D04333|JVBPAL DNA-packaging protein A - phage lambda Length = 641	gi|215106	2	349	95	95	HBGBT12
337	HBGBH53R	Actin [Drosophila melanogaster] >pir|S14851|S14851 actin - fruit fly (Drosophila melanogaster) >sp|Q24228|Q24228 ACTIN. Length = 100	gi|7550	2	445	93	97	HBGBH53

338	HTXPI29R	aldolase A (EC 4.1.3.13) [Homo sapiens] >gi|28597 aldolase A (AA 1-364) [Homo sapiens] >pir|S14084|ADHUA fructose-bisphosphate aldolase (EC 4.1.2.13) A - human >sp|P04075|ALFA_HUMAN FRUCTOSE-BISPHOSPHATE ALDOLASE A (EC 4.1.2.13) (MUSCLE-TYPE ALDOLASE). {S	gi|178351	1	453	86	86	HTXPI29
339	HOFMG33R	ATPase [Equus caballus] >sp|P48662|ATP6_HORSE ATP SYNTHASE A CHAIN (EC 3.6.1.34) (PROTEIN 6). Length = 226	gi|577577	28	309	57	62	HOFMG33
340	HCGAC11R			1	345			HCGAC11
341	HCIAC54R			37	168			HCIAC54
342	HBGAA54R			1	282			HBGAA54
343	HAOMC34R	calpactin I heavy chain (p36) [Bos taurus] >pir|A03081|LUBO36 annexin II - bovine >sp|P04272|ANX2_BOVIN ANNEXIN II (LIPOCORTIN II) (CALPACTIN I HEAVY CHAIN) (CHROMOBINDIN 8) (P36) (PROTEIN I) (PLACENTAL ANTICOAGULANT PROTEIN IV) (PAP-IV). {SUB 2-339} Leng	gi|162779	2	115	73	80	HAOMC34
344	H2LAU88R	copine I [Homo sapiens] >sp|Q99829|Q99829 COPINE I. Length = 537	gi|1791257	1	576	95	95	H2LAU88
345	HDPJR77R	DNA topoisomerase II [Homo sapiens] >gi|38325 DNA topoisomerase II [Homo sapiens] {SUB 448-681} Length = 1031	gi|288565	3	311	100	100	HDPJR77

346	HTTIO41R	docking protein [Homo sapiens] >pir|A29440|A29440 signal recognition particle receptor - human Length = 638	gi|30866	90	404	94	95	HTTIO41
347	H2CBU29R	electron transport flavoprotein [Homo sapiens] >pir|A31998|A31998 electron transfer flavoprotein alpha chain precursor - human >sp|P13804|ETFA_HUMAN ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT PRECURSOR (ALPHA-ETF). >gnl|PID|e1331769 (AJ224002) electron	gi|182251	2	442	100	100	H2CBU29
348	HBMVA11R	GARS protein [Homo sapiens] >sp|Q15374|Q15374 GARS PROTEIN. Length = 433	gnl|PID|d100 7383	1	108	81	84	HBMVA11
349	HDPUL86R	GC kinase [Homo sapiens] >pir|A53714|A53714 protein kinase (EC 2.7.1.37) BL44 - human >sp|Q12851|Q12851 GC KINASE. Length = 819	gi|531820	3	317	64	65	HDPUL86
350	HTXNT16R	GTP-binding protein [Homo sapiens] >gi|577779 GTP-binding protein [Homo sapiens] >pir|A55014|A55014 GTP-binding protein - human >sp|P55039|DRG2_HUMAN DEVELOPMENTALLY REGULATED GTP-BINDING PROTEIN DRG2. Length = 364	gi|577779	2	463	100	100	HTXNT16
351	HBGAA13R	H (tail component;853) [Bacteriophage lambda] >pir|G43008|TLBPHL minor tail protein precursor H - phage lambda Length = 853	gi|215120	1	267	97	97	HBGAA13

352	HLXNA54R	heat shock protein HSP27 [Homo sapiens] >gi|433598 28 kDa heat shock protein [Homo sapiens] >gi|1913885 heat shock protein [Homo sapiens] >pir|S12102|HHHU27 heat shock protein 27 - human >sp|G248440|G248440 28 KDA HEAT SHOCK PROTEIN HOMOLOG FRAGMENT 2. {S	gi|32478	2	256	98	98	HLXNA54
353	HCHOH37R	Hep27 protein [Homo sapiens] >pir|S66665|S66665 nuclear protein Hep27 - human >sp|Q13268|HE27_HUMAN HEP27 PROTEIN (PROTEIN D). {SUB 24-280} Length = 280	gi|1079566	337	564	75	81	HCHOH37
354	H2LAX93R	histone H2B [Gallus gallus] >gi|63434 histone H2B [Gallus gallus] >gi|63452 histone H2B (AA 1 - 126) [Gallus gallus] >gi|63456 histone H2B (AA 1 - 126) [Gallus gallus] >gi|63458 histone H2B [Gallus gallus] >gi|63460 histone H2B (AA 1 - 126) [Gallus gallus	gi|211845	191	505	89	96	H2LAX93
355	HWAFW10R	homologue to elongation factor 1-gamma from A.salina [Homo sapiens] >gi|31104 elongation factor-1-gamma [Homo sapiens] >pir|S22655|S22655 translation elongation factor eEF-1 gamma chain - human >sp|P26641|EF1G_HUMAN ELONGATION FACTOR 1-GAMMA (EF-1-GAMMA).	gi|31102	3	434	98	98	HWAFW10

356	HBNAB19R	human complement C1r [Homo sapiens] >pir|A24170|C1HURB complement subcomponent C1r (EC 3.4.21.41) precursor - human >sp|P00736|C1R_HUMAN COMPLEMENT C1R COMPONENT PRECURSOR (EC 3.4.21.41). Length = 705	gi|179644	2	193	98	98	HBNAB19
357	HBGDD17R	hypothetical protein [Escherichia coli] >gi|1786774 (AE000161) orf, hypothetical protein [Escherichia coli] >pir|G64788|G64788 hypothetical protein b0561 - Escherichia coli (strain K-12) Length = 247	gi|1778474	1	207	98	98	HBGDD17
358	HBIAB72R	hypoxanthine phosphoribosyltransferase [Sus scrofa] >sp|P79306|P79306 HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE (FRAGMENT). Length = 85	gnl|PID|e291969	2	169	81	86	HBIAB72
359	HFIEH41R	interferon-gamma induced protein [Homo sapiens] >pir|I54501|I54501 interferon gamma-induced protein IFI 16 - human >sp|Q16666|IF16_HUMAN GAMMA-INTERFERON-INDUCIBLE PROTEIN IFI-16 (INTERFERON-INDUCIBLE MYELOID DIFFERENTIATION TRANSCRIPTIONAL ACTIVATOR). Le	gi|184569	5	406	96	97	HFIEH41
360	H2CBB43R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir|D43009|QSBPL host specificity protein J - phage lambda Length = 1132	gi|215125	2	400	99	99	H2CBB43

361	H2CBQ77R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir|D43009|QSBPL host specificity protein J - phage lambda Length = 1132	gi|215125	3	272	97	97	H2CBQ77
362	HATAO24R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir|D43009|QSBPL host specificity protein J - phage lambda Length = 1132	gi|215125	2	247	71	71	HATAO24
363	HOEMK06R	K (tail component;199) [Bacteriophage lambda] >pir|H43009|TJBPKL tail assembly protein K - phage lambda Length = 199	gi|215123	3	149	97	97	HOEMK06
364	HADCH03R	mitochondrial acetoacetyl-CoA thiolase precursor [Homo sapiens] Length = 427	gnl|PID|d1014983	2	256	83	83	HADCH03
365	HCHAG30R	Mta1 [Rattus norvegicus] >pir|A54766|A54766 metastasis-associated protein mta-1 - rat >sp|Q62599|MTA1_RAT METASTASIS-ASSOCIATED PROTEIN MTA1. Length = 703	gi|595253	2	271	92	92	HCHAG30
366	HOFAD96R	NADH dehydrogenase subunit 4L [Felis catus] >sp|P48931|NULM_FELCA NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 4L (EC 1.6.5.3). Length = 98	gi|1098532	2	253	50	52	HOFAD96
367	H2CBX07R	Nin 221 (pept unknown;221) [Bacteriophage lambda] >pir|G43011|Q1BP1L multiple specificity phosphoprotein phosphatase (EC 3.1.3.-) - phage lambda >sp|P03772|PP_LAMBD SERINE/THREONINE PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 221	gi|215160	2	184	100	100	H2CBX07

368	HDPLN02R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi|1699027	149	454	90	90	HDPLN02
369	HT4FU27R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi|1699027	96	287	95	95	HT4FU27
370	HAEAI26R	open reading frame A; putative [Homo sapiens] Length = 84	gi|190369	109	291	78	80	HAEAI26
371	HCDAR56R	p23 [Homo sapiens] >pir|A56211|A56211 progesterone receptor-related protein p23 - human >sp|Q15185|Q15185 (P23). Length = 160	gi|438652	2	208	90	92	HCDAR56
372	HCDCW35R	precursor [Homo sapiens] Length = 631	gi|36049	3	155	78	84	HCDCW35
373	H2CBN76R	proteasome subunit C5 [Homo sapiens] >gnl|PID|e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir|S15973|SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp|P20618|PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gnl|PID|d100 1116	3	464	99	99	H2CBN76
374	HAGFX49R	proteasome subunit C5 [Homo sapiens] >gnl|PID|e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir|S15973|SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp|P20618|PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gnl|PID|d100 1116	1	288	98	100	HAGFX49

375	HNEEG64R	put. major coat protein (AA 1-341) [Bacteriophage phi-80] >pir|S03314|VHBP80 major capsid protein - phage phi-80 >sp|P05481|HEAD_BPPH8 MAJOR HEAD PROTEIN (GPE) (GP5) (MAJOR COAT PROTEIN). Length = 341	gi|15769	17	232	81	97	HNEEG64
376	HTXKR32R	putative nucleotide-binding protein [Homo sapiens] >pir|JC4010|JC4010 nucleotide-binding protein - human >sp|P53384|NBP_HUMAN NUCLEOTIDE-BINDING PROTEIN (NBP). Length = 320	gi|515644	3	374	100	100	HTXKR32
377	HAIBZ58R	putative start codon [Homo sapiens] Length = 210	gi|895845	2	433	65	65	HAIBZ58
378	H6EAF46R	rexa (exclusion;279) [Bacteriophage lambda] >gi|15068 reading frame (rex1 protein) [Bacteriophage 434] >pir|E43010|IMBPAL rexA protein - phage lambda Length = 279	gi|215146	43	333	92	93	H6EAF46
379	H2LAW60R	ribosomal protein L27a [Homo sapiens] >pir|S55914|S55914 ribosomal protein L27a - human Length = 148	gi|550017	3	545	88	88	H2LAW60
380	H2LAK40R	ribosomal protein L31 [Sus scrofa] >gi|36130 ribosomal protein L31 (AA 1-125) [Homo sapiens] >gi|57115 ribosomal protein L31 (AA 1-125) [Rattus norvegicus] >pir|S05576|R5HU31 ribosomal protein L31 - human >pir|A26417|R5RT31 ribosomal protein L31 - rat >gn	gnl|PID|e2764 36	76	483	77	80	H2LAK40

381	H2LAY71R	ribosomal protein L35 [Homo sapiens] >pir|G01477|G01477 ribosomal protein L35 - human Length = 123	gi|562074	70	495	100	100	H2LAY71
382	HCHAH62R	ribosomal protein L8 [Homo sapiens] >gi|57704 ribosomal protein L8 [Rattus rattus] >gi|1527178 ribosomal protein L8 [Mus musculus] >pir|JU0177|R5RTL8 ribosomal protein L8, cytosolic - rat >pir|JN0923|JN0923 ribosomal protein L8, cytosolic - human >gi|3851	gi|433899	1	222	76	76	HCHAH62
383	H6EEF31R	ribosomal protein S2 [Rattus norvegicus] >sp|O55211|O55211 RIBOSOMAL PROTEIN S2. Length = 257	gi|2920825	1	300	89	91	H6EEF31
384	HDPBT55R	RNAse L inhibitor [Mus musculus] >sp|O88793|O88793 RNASE L INHIBITOR. Length = 599	gi|3273417	71	127	81	86	HDPBT55
385	HASAW80R	S.macroura Wilms tumour protein [Sminthopsis macroura] Length = 239	gi|987118	1	162	90	98	HASAW80
386	HCHAF25R	SSR alpha subunit [Homo sapiens] >pir|I38246|I38246 SSR alpha subunit - human Length = 286	gi|551638	2	421	95	95	HCHAF25
387	HLTHH84R	UMP synthase [Homo sapiens] >pir|A30148|A30148 UMP synthase - human Length = 480	gi|340168	2	391	99	99	HLTHH84
388	H2CBU20R			39	143			H2CBU20
389	HADAA62R			3	218			HADAA62
390	HADDC09R			16	174			HADDC09
391	HAIAB75R			2	211			HAIAB75

392	HAMGA37R	3	119	HAMGA37
393	HAQAI10R	1	81	HAQAI10
394	HBFME95R	3	218	HBFME95
395	HBGBH24R	1	81	HBGBH24
396	HBGBT78R	1	69	HBGBT78
397	HBGCB06R	3	140	HBGCB06
398	HBGDO01R	1	156	HBGDO01
399	HBIBJ73R	3	341	HBIBJ73
400	HBJLE85R	3	398	HBJLE85
401	HBNAD53R	2	187	HBNAD53
402	HBNAT63R	54	173	HBNAT63
403	HCE4H65R	2	193	HCE4H65
404	HCFLJ44R	92	274	HCFLJ44
405	HCHMW05R	3	221	HCHMW05
406	HCHNR50R	2	103	HCHNR50
407	HE8DS01R	2	64	HE8DS01
408	HFEBP31R	109	276	HFEBP31

			6	167	HLDXE36
			181	414	HLTGV28
			42	308	HODFW25
			1	129	HOEMQ91
			57	386	HOGBG56
			2	151	HOSMT44
			51	191	HRAEE04
			3	272	HULFN65
			1	153	HWLVW23
			149	289	HWLWE77
409	HLDXE36R				
410	HLTGV28R				
411	HODFW25R				
412	HOEMQ91R				
413	HOGBG56R				
414	HOSMT44R				
415	HRAEE04R				
416	HULFN65R				
417	HWLVW23R				
418	HWLWE77R				

The first column of Table 1 shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention.

The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:418) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ

ID NO:418 through SEQ ID NO:836) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and decribed further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which bind specifically to the breast/ovarian cancer antigen polypeptides, or fragments thereof, and/or to the breast/ovarian cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

Table 2

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as "the deposits" herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the

ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be

included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

Table 3

Sequence/ Contig ID	General formula	Genbank Accession No.
419266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1899 of SEQ ID NO:1, b is an integer of 15 to 1913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14.	T68585, T68665, T86313, T86314, R12356, R31374, R32873, R37282, R84617, R85369, R99171, H48474, N23871, N58201, N74557, W90334, AA031318, AA031427, AA130231, AA256587
429114	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:2, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14.	R20542, R42676, R42676, R20542, R61501, H08662, H77556, H97365, N24198, N33135, N74546, N93573, W02941, W52194, AA004624, AA004721, AA046710, AA235395, AA235479
506777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 340 of SEQ ID NO:3, b is an integer of 15 to 354, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14.	
508678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 500 of SEQ ID NO:4, b is an integer of 15 to 514, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14.	W37175, AA121532, AA127694
508968	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T71941, T94428, T94514, H02313, N26913, N47870, N66244, N92418, W31301, W42459, W42564, AA084031, AA126786, AA258050, AA459772

	formula of a-b, where a is any integer between 1 to 2021 of SEQ ID NO:5, b is an integer of 15 to 2035, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14.	
509029	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:6, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14.	R11213, R11271, H14072, H14071, H51531, H66637, H66636, W23707, W35307, AA025586, AA025710, AA058796, AA113917
519726	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 610 of SEQ ID NO:7, b is an integer of 15 to 624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14.	AA236015, AA236085, AA256106
522632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 287 of SEQ ID NO:8, b is an integer of 15 to 301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14.	
524655	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 672 of SEQ ID NO:9, b is an integer of 15 to 686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14.	T66495, R15869, R39696, H16266, H20784, H22599, N68150, W58001, W57856
525847	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:10, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14.	
530306	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:11, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.	
532818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 429 of SEQ ID NO:12, b is an integer of 15 to 443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.	AA188990, AA191040
533385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2424 of SEQ ID NO:13, b is an integer of 15 to 2438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.	
533532	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2333 of SEQ ID NO:14, b is an integer of 15 to 2347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	T94240, T77619, R13236, R17515, R33142, R33294, R39249, R40318, R42609, R42609, R40318, R75952, H03594, H12337, H12391, H70913, H70916, H70996, H71001, H87858, H70913, N21374, N31326, N35068, N35435, N43807, N45045, W46431, W46486, W51917, AA019546, AA018858, AA056764, AA056767, AA058441, AA058445, AA083228, AA083269, AA115939, AA122236, AA147307, AA159802,

	NO:14, and where b is greater than or equal to a + 14.	AA165015, AA165642, AA181869, AA186834, AA252269, AA255892, AA463239, AA463240
534852	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:15, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.	T55469, T63434, R10603, R10604, H50597, H92640, H94634, W39162, W93243, W94634, W94719, N90240, AA053667, AA167312, AA253414, AA253389
537910	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:16, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.	R23785
538460	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:17, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.	R13084, R40514, R40514, R55303, R55402, W67446
539577	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 832 of SEQ ID NO:18, b is an integer of 15 to 846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.	T49208, N35488, AA088419, AA127572, AA127649, AA156316, AA169250
548379	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2178 of SEQ ID NO:19, b	R23778, H70824

	is an integer of 15 to 2192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.	
548489	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 997 of SEQ ID NO:20, b is an integer of 15 to 1011, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.	T49861, T49862, T56225, T56367, T72170, T72948, T92867, T74728, R08625, R08719, R17408, R24674, R25174, R25378, R25997, R26800, R28401, R31330, R31589, R42642, R45259, R42642, R45259, R62552, R62553, R66386, R67726, R68781, R68878, H25120, H25121, H41115, H41190, H41191, R84227, R87629, H53386, H64419, H64476, H72640, H72641, H64419, H99301, N22341, N25846, N29370, N29843, N47918, N57261, N59763, N63813, N94171, W23786, W45524, W72111, W77797, AA010718, AA011164, AA033553, AA033554, AA062727, AA062741, AA062784, AA069811, AA075470, AA075471, AA081844, AA083492, AA084442, AA100358, AA126263, AA126354, AA136544, AA136648, AA146862, AA146863, AA179509, AA179540, AA179775, AA180492, AA181719, AA188903, AA189140, AA226959, AA227247
548595	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2005 of SEQ ID NO:21, b is an integer of 15 to 2019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.	T61537, T69836, R10679, R42501, R46798, R42501, R46798, H05289, H05822, H12239, H16816, H40312, R86905, R86985, N21432, N73268, W73102, N91565, AA033533, AA053026, AA121547, AA127684, AA190356, AA195451, AA226965, AA232522, AA258142
549337	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2008 of SEQ ID NO:22, b is an integer of 15 to 2022, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.	
549777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:23, b	T81557, R27931, R38730, R39493, R39494, R66845, R67942, R69099, R69214, R69613, R69703, R69740, R72430, R72478, R73090, R73091, R73872, R73955, R82662, R82715, H01096, H01097, H72113, N76139, W58493, W72884, W74409, W94644, W92532,

	is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.	AA022916, AA022917, AA039661, AA039660, AA043439, AA054965, AA152376, AA148360, AA181225, AA188435
553091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2584 of SEQ ID NO:24, b is an integer of 15 to 2598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.	
553827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 397 of SEQ ID NO:25, b is an integer of 15 to 411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.	
556350	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:26, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.	T70920, R01856, R37402, H21077, H21531, R94734, N29364, N32255, N80553, W07675, W58340, W58661, W67208, W67352, AA039658, AA039659, AA046392, AA055650, AA058365, AA070442, AA088882, AA102056, AA134144, AA165363, AA171617, AA173761, AA173771, AA252260, AA464575, AA464679
556351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1889 of SEQ ID NO:27, b is an integer of 15 to 1903, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.	T70981, R01855, R13494, H21076, H24431, H24460, R94817, N47912, AA040086, AA040133, AA055706, AA056162, AA058484, AA102055, AA102304, AA130304, AA173608, AA195879
557007	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H13846, H13894, H16354, H20742, H20743, R97935, R97936, H87445, N29633, AA015991, AA045671, AA045670, AA099154, AA099252

	sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:28, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.	
558140	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1313 of SEQ ID NO:29, b is an integer of 15 to 1327, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.	T62991, W58535, W58500, AA053629, AA083878, AA112892, AA157250, AA157345, AA194089, AA253436, AA250750
558456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:30, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.	
558708	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:31, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.	R38385, W24640, W48793, W49619
574789	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:32, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.	N49156

578203	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 541 of SEQ ID NO:33, b is an integer of 15 to 555, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.	AA149853
585385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 333 of SEQ ID NO:34, b is an integer of 15 to 347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.	
588869	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 736 of SEQ ID NO:35, b is an integer of 15 to 750, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.	
597076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:36, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.	
598656	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1521 of SEQ ID NO:37, b is an integer of 15 to 1535, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.	
611880	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 281 of SEQ ID NO:38, b is an integer of 15 to 295, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.	
614329	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1286 of SEQ ID NO:39, b is an integer of 15 to 1300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.	T49777, T51334, T49778, T66835, T66836, T78401, R33579, R33684, R34361, R34476, R72556, R75702, H01591, H02719, H13232, H13599, H13942, H13943, H63376, H80729, H80730, H89353, H89539, H99395, N26995, N32930, N40116, N42081, N50408, N50460, N63978, N67308, N92847, W46413, AA126994, AA128141, AA146958, AA146957, AA425764
616066	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 201 of SEQ ID NO:40, b is an integer of 15 to 215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.	
620956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:41, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.	
621889	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 411 of SEQ ID NO:42, b is an integer of 15 to 425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.	
624017	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1173 of SEQ ID NO:43, b is an integer of 15 to 1187, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.	T61010, AA071044, AA088260, AA098798, AA102017, AA100707, AA111883, AA113305, AA121495, AA133235, AA131438, AA132011, AA132866, AA143457, AA146581, AA146805, AA146928, AA155613, AA155609, AA158090, AA158263, AA164694, AA165591, AA176429, AA226820
651784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:44, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.	W32583, W68240, W94174, AA251670, AA252011, AA252266, AA425209
651826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1485 of SEQ ID NO:45, b is an integer of 15 to 1499, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.	T47384, T47385, T60137, T60194, T71947, T95050, T95146, R25340, R25476, R26117, R26301, R27566, R27664, R28180, R33393, R35872, R35873, R36483, R48329, R48438, R62139, R62244, R66007, R66008, R66764, R70718, R70719, R73674, R73761, R74132, R76569, R76643, R77265, R77312, R78827, R79686, R79687, R81316, R81751, H00804, H00891, H01415, H01416, H02522, H03673, H13925, H13926, H24743, H26369, H26727, H26728, H27132, H27480, H27663, H28192, H28235, H41929, H41977, H42604, H43209, H43258, H45278, H45348, H53585, H53906, H61785, H61786, H78337, H78338, H87337, H87871, H95183, N27090, N27092, N40499, N40502, N99158, W24165, W60193, AA039817, AA041344, AA074512, AA079058, AA079156, AA079157, AA085829, AA085974, AA100095, AA113304, AA142843, AA149898, AA156331, AA157820, AA157895, AA158552, AA159177, AA176093, AA179607, AA179608, AA176333, AA187637, AA186769, AA188622, AA188742, AA188975
653282	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 379 of SEQ ID NO:46, b is an integer of 15 to 393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.	
657122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 224 of SEQ ID NO:47, b is an integer of 15 to 238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.	
661442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 925 of SEQ ID NO:48, b is an integer of 15 to 939, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.	R18101, AA424721
664914	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1757 of SEQ ID NO:49, b is an integer of 15 to 1771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.	T86944, T87027, R11421, T81153, T81380, R17243, R17453, R19171, R27826, R27927, R35295, R35940, R41854, R42800, R48191, R48192, R49457, R51209, R52247, R53413, R41854, R42800, R49457, R55257, R55475, R59472, R71390, R81811, R81915, H05137, H07974, H30702, H42552, H57923, H58015, N71127, N74282, N75329, N93224, W01557, W04382, W04780, W23438, W35253, W38865, AA176204, AA194869, AA199875, AA251414
666654	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:50, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:50, and where b is greater than or equal to a + 14.	
667084	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1621 of SEQ ID NO:51, b is an integer of 15 to 1635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.	R71869, R71870, H22387, H27160, H46592, H61204, H62108, N25274, N94410, AA026642, AA069188, AA069189, AA076423, AA076388, AA076533, AA076540, AA122346, AA121039, AA121092, AA133121, AA143471, AA143470, AA143728, AA156363, AA156404, AA158498, AA159190, AA159201, AA159286, AA160335, AA159837, AA159573, AA160367, AA159548, AA160456, AA160697, AA160789, AA179329, AA181540, AA182669, AA186881, AA186887, AA188535, AA188540, AA190669, AA190973, AA191557, AA235457, AA458511, AA418203
667380	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:52, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.	T87574, R10276, R10277, T79847, R49790, R49832, R59538, R59539, R86940, R87067, R87722, R98577, R98578, R99022, R99795, H72692, H93036, H93942, H93941, N54059, N62326, N64719, N66726, N73888, N74171, N91734, N93505, W02054, W03949, W04337, W21317, AA192562, AA192563, AA223984, AA224049
669530	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:53, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.	T49160, T49161, H41659, R88196, W60799, W60930, AA046915, AA046972, AA069703, AA464334
671315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1930 of SEQ ID NO:54, b is an integer of 15 to 1944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.	
671993	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 980 of SEQ ID NO:55, b is an integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.	
674618	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 314 of SEQ ID NO:56, b is an integer of 15 to 328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.	
675027	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:57, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.	T86474, AA133454, AA203346
677202	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:58, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.	T47486, T47487, T47666, T50413, T50493, T50519, T51852, T53234, T57067, T60776, T40856, T93579, T94432, T94435, T96391, R43542, R43542, H21618, H73240, H88867, H88868, H89122, H88868, H89122, N21997, N22243, N22815, N45720, N48998, N52063, N59239, N62103, N66419, N66708, N66782, N67139, N67283, N67447, N68047, N70159, N71198, N74676, N76707, N78333, N80016, N92971, N93518, W05738, W45694, W48845, W80602, AA057801, AA063330, AA064827, AA065165, AA065178, AA065179, AA069552, AA070491, AA070949, AA070969, AA071333, AA071358, AA074331, AA081280, AA111928, AA112051, AA132018, AA132121, AA147357, AA157065, AA157085, AA157890, AA160054, AA181729, AA182765, AA187698, AA186444, AA196168, AA196244, AA224187
678504	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:59, b is	

	an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.	
678985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:60, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.	
682161	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:61, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.	
683476	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:62, b is an integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.	
691146	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:63, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.	T48865, T48866, T48901, T47562, T48902, T54258, T54365, T69783, T70768, R08012, R09058, R09059, T83437, T84082, T99021, R09059, R19174, R21551, R22562, R28286, R48757, R48758, R49683, R49683, R62406, R62407, R70222, R75607, R77000, R78400, R78401, R80802, H02840, H03734, H24549, H26291, H26447, H27912, H43630, H47817, R83903, R83904, R94147, H49533, H49773, H50716, H50820, H87446, H87553, H93471, H93472, H98814, N22867, N32137, N32762, N34334, N35009, N36932, N43763, N46205, N52251, N56805, N72290, N95794, W02713, W02886, W17176, W24905, W25571, W25688,

		W67795, W72687, W72962, W77793, W79704, W81376, W86301, W86316, AA025519, AA025959, AA026653, AA029556, AA029704, AA079472, AA121306, AA136679, AA148681, AA148680, AA181745, AA425923
693589	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 404 of SEQ ID NO:64, b is an integer of 15 to 418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.	
694991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2822 of SEQ ID NO:65, b is an integer of 15 to 2836, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.	
698303	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2291 of SEQ ID NO:66, b is an integer of 15 to 2305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.	T83582, T84417, T85606, R66380, R67111, R76298, H96019, H96020, N25659, N25661, N34260, N34263, N70618, W05500, W15421, W23670, W39659, AA015855, AA033569, AA033570, AA044566, AA044583, AA178933, AA179025
698669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:67, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.	T47115, T47116, R48786, R48893, R55495, R71847, R78934, R79033, R82776, H26587, H27077, R97760, H59232, H79115, H79116, N22948, N23658, N26858, N28757, N39967, N71599, W24648, W60157, W67490, W67491, W67815, W72921, W94215, AA009634, AA026899, AA026900, AA029244, AA029040, AA031846, AA031847, AA032073, AA034285, AA034992, AA036865, AA037006, AA040908, AA039990, AA040521, AA040522, AA040773, AA043726, AA044071, AA044182, AA042948, AA043067, AA046606, AA046721, AA062914, AA074334, AA076039, AA076203, AA079763, AA079764, AA082550, AA085926, AA099318,

		AA099836, AA102385, AA101039, AA101040, AA112571, AA112572, AA114828, AA114951, AA128001, AA128082, AA126986, AA128134, AA128459, AA129910, AA131403, AA131503, AA147437, AA147438, AA150961, AA151051, AA156785, AA156855, AA157912, AA157913, AA158544, AA158545, AA158554, AA158553, AA211822, AA460840, AA461144
705696	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:68, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.	H20141, H20156, H20236, H20250, H49965, H50007, H50487, W92252, AA045116, AA134141, AA142968
706393	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1136 of SEQ ID NO:69, b is an integer of 15 to 1150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.	T48975, T51242, T51357, T59673, T59807, T62725, T62875, T72330, T97577, R01168, R21893, R22365, R35745, R41863, R41863, R63676, R65881, R72862, R73334, R75659, R75767, H02871, H03430, H03512, H14924, H23660, H30020, H30277, H39675, H40069, H40278, H40526, H41667, H41700, H43170, H43670, H45130, H45172, H45173, H45433, H46542, H46952, H46953, H62390, H78695, H78777, H84781, H85405, H92309, N20534, N33402, N38945, N57790, N57945, N59752, W94488, W94489, AA044423, AA043057, AA081370, AA081371, AA099447, AA112623, AA112622, AA143199, AA143214, AA149467, AA149553, AA157049, AA157201, AA157952, AA157953, AA158049, AA158435, AA158837, AA158841, AA161074, AA161078, AA180395, AA251447, AA419021, AA428783, AA429093
707357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 330 of SEQ ID NO:70, b is an integer of 15 to 344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.	
707360	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 434 of SEQ ID NO:71, b is an integer of 15 to 448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.	
707375	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2811 of SEQ ID NO:72, b is an integer of 15 to 2825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.	T54138, T65139, T65330, T80324, T83140, R00512, R00612, R19513, R31469, R31470, R47795, R77921, R78022, R80012, H02327, H02429, H06404, H06405, H08607, H08608, H14264, H18370, H19266, H19267, H21399, H21471, H47094, H47185, R85467, R87496, R87501, R87581, R88189, R88226, R88227, N23376, N32357, N58463, N66212, N93661, N99103, W19083, W24383, W68601, W68602, W68723, W68745, AA016149, AA040296, AA056973, AA135439, AA135519, AA135580, AA135856, AA158858, AA161122, AA226730, AA226764, AA227471, AA227481, AA232259
707754	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:73, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.	
711172	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:74, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.	
712248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 363 of SEQ ID NO:75, b is an integer of 15 to 377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or	

	equal to a + 14.	
715445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2056 of SEQ ID NO:76, b is an integer of 15 to 2070, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.	T88778, T97557, T97604, R17189, R27615, R30849, R41740, R48616, R41740, H12351, R93768, R98882, R98972, H59983, N23156, N32736, N34539, N55086, N62785, N67224, N77297, N78823, N79734, W07252, W90651, AA037793, AA037794, AA055196, AA055286, AA113425, AA233917, AA234165, AA258602, AA258548, AA426581, AA429080
716362	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 983 of SEQ ID NO:77, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.	
716835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:78, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.	
716947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 546 of SEQ ID NO:79, b is an integer of 15 to 560, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.	
717685	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3189 of SEQ ID NO:80, b is an integer of 15 to 3203, where both a	T54040, N35800, W45088, AA122232, AA121109, AA126030, AA126152, AA155618, AA155656

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.	
719755	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1696 of SEQ ID NO:81, b is an integer of 15 to 1710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.	
720389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:82, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.	
720903	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:83, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.	
721348	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2789 of SEQ ID NO:84, b is an integer of 15 to 2803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.	
721562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 1264 of SEQ ID NO:85, b is an integer of 15 to 1278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.	
722775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2571 of SEQ ID NO:86, b is an integer of 15 to 2585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.	
724463	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 371 of SEQ ID NO:87, b is an integer of 15 to 385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.	
727501	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2486 of SEQ ID NO:88, b is an integer of 15 to 2500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.	
728418	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:89, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.	
728920	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:90, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.	
732958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 773 of SEQ ID NO:91, b is an integer of 15 to 787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.	
733134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1643 of SEQ ID NO:92, b is an integer of 15 to 1657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.	T49547, T49558, T49559, T49560, T49561, T49649, T49650, T70062, T70129, T75532, T95137, R17573, T27052, R19790, R42912, R52618, R53272, R42912, R59922, R59923, R65930, H08841, H08925, H47546, H47547, H47774, H47784, H48119, H64949, H64950, H69959, H69960, H80517, H80569, H81281, H81337, H87618, H87619, H88959, H89042, H95657, H95712, H95729, H88959, H98860, N20108, N23582, N27446, N34733, N49675, N51841, N75517, N78965, N93975, W05310, W17334, W40344, W52084, W52929, W72818, W72819, W86046, W92307, W92294, AA009783, AA009892, AA022930, AA022980, AA024699, AA024734, AA037408, AA045887, AA045888, AA062821, AA081026, AA082088, AA082420, AA102801, AA199861, AA199931, AA220961, AA223217, AA223456, AA224153, AA224177, AA224137, AA224138, AA224341, AA232349, AA232533, AA232117, AA458900, AA459095, AA463299
734099	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 471 of SEQ ID NO:93, b is an integer of 15 to 485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or	R22895, H87448

	equal to a + 14.	
734599	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 750 of SEQ ID NO:94, b is an integer of 15 to 764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.	
736019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 693 of SEQ ID NO:95, b is an integer of 15 to 707, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.	T41219, T50359, T56829, T58426, T58458, T60928, T60984, T64158, T64287, R27157, H03484, H03579, H22546, H22547, H28310, H44067, H44146, R83796, H48481, H48645, H57243, H66162, H66163, H82370, N21110, N21188, N27461, N29155, N29743, N31124, N32398, N39884, N56818, N57165, N57228, N57403, N68904, N73978, N77833, N93027, N93818, N67112, W00894, W00923, W02234, W16676, W21379, W44969, AA064843, AA070697, AA070876, AA071332, AA071265, AA076379, AA076308, AA079524, AA079572, AA081231, AA081401, AA083774, AA083775, AA130308, AA130309, AA132056, AA132160, AA143132, AA146882, AA146883, AA165057, AA164722, AA166939, AA181133, AA187371, AA187804, AA188118, AA186447, AA186448, AA187105, AA187150, AA188273
738268	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:96, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.	T48287, T48288, T54477, T54511, R34064, R36907, R49496, R49496, R75625, R75724, H12225, H16384, H19466, H19543, H42166, H42988, H54780, H99297, N22733, N26471, N74933, N93468, W15461, W47542, W47590, N90997, AA010700, AA010701, AA056728, AA088699, AA126219, AA132934, AA156291, AA165516, AA165558, AA176293, AA173448, AA189056, AA233515, AA459831, AA460011
738911	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:97, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.	H22593, H52836

739226	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 235 of SEQ ID NO:98, b is an integer of 15 to 249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.	T57824, N63155, AA027845
739527	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:99, b is an integer of 15 to 752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.	
740710	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3045 of SEQ ID NO:100, b is an integer of 15 to 3059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.	
742980	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1668 of SEQ ID NO:101, b is an integer of 15 to 1682, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.	T71993, R12901, R40053, H14591, H14696, R83485, H50584, H50585, H89958, H89966, H89973, H89980, N26005, N34777, N36638, N36637, N44503, N67682, N76121, N79613, W03491, W05571, W31276, W49653, W49727, AA009708, AA009798, AA035612, AA042894, AA043030, AA062953, AA115370, AA133278, AA181268, AA181269, AA193206
744331	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:102, b is an integer of 15 to 938, where both a and b correspond to the positions of	R25354, R49789, R71735, R71740, H73502, H79224, H87423, H99515, H99516, N24751, N32707, N44511, N52325, N67764, N75095, N93879, W40372, W69127, W69094, W74698, W74736, AA026984, AA035176, AA149088, AA262739, AA464357, AA430724

	nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.	
744751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1998 of SEQ ID NO:103, b is an integer of 15 to 2012, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.	
745750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:104, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.	
746285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2283 of SEQ ID NO:105, b is an integer of 15 to 2297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.	T87719, T87928, R99975, R99976, H64714, H65205, H92423, H65205, N47296, N48612, N58085, N58926, N64294, N64508, N72401, N80294, N93405, W04791, W21447, W94582, W95317, AA024856, AA024939, AA037672, AA037673, AA070416, AA075508, AA075507, AA101263, AA148029, AA147953, AA169726, AA171461, AA173095, AA464821
746416	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO:106, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.	
747851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	N44767, W44754

	between 1 to 1005 of SEQ ID NO:107, b is an integer of 15 to 1019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.	
750632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 697 of SEQ ID NO:108, b is an integer of 15 to 711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.	H48882, W23677, W35110, AA133857
751315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:109, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.	
754009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 781 of SEQ ID NO:110, b is an integer of 15 to 795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.	
754634	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1318 of SEQ ID NO:111, b is an integer of 15 to 1332, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.	N21429
756637	Preferably excluded from the present invention are one or more	N44651, W76461

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:112, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.	
756833	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1676 of SEQ ID NO:113, b is an integer of 15 to 1690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.	
756878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 606 of SEQ ID NO:114, b is an integer of 15 to 620, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.	R12122
757332	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:115, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.	
760835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:116, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or	

	equal to a + 14.	
761760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 714 of SEQ ID NO:117, b is an integer of 15 to 728, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.	
762520	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:118, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.	T86617, T86618, R47814, R49961, R71921, R71968, H28225, H28275, R94939, R95025, R97173, R97174, R99726, R99904, H52435, H52436, H58879, H58880, H66345, H66395, H80709, H80710, W87663, W87664, AA046620, AA046867, AA055456, AA102380, AA121314, AA150579, AA197300
764461	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 197 of SEQ ID NO:119, b is an integer of 15 to 211, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.	
764517	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1294 of SEQ ID NO:120, b is an integer of 15 to 1308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.	
765132	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2502 of SEQ ID NO:121, b is an integer of 15 to 2516, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.	
765667	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1125 of SEQ ID NO:122, b is an integer of 15 to 1139, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.	T81691, N27595
767113	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2100 of SEQ ID NO:123, b is an integer of 15 to 2114, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.	
767204	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 569 of SEQ ID NO:124, b is an integer of 15 to 583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.	
767400	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:125, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.	
767962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T59753, R21255, R21256, R23274, R23364, R71913, R71956, H12633, H12686, H99087, N26954, N33518, N43798, N62998, N66835, N71124, N71156, N74144, N79907, W01554,

	formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:126, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.	W05537, W19994, W44368, W46357, W46193, W47163, W47284, W52537, W55854, W80804, W80878, W92021, W92022, N90420, AA002178, AA022578, AA022579, AA029899, AA029987, AA034181, AA036856, AA036913, AA043237, AA043566, AA071518, AA082340, AA122159, AA120962, AA146944, AA147449, AA148081, AA151266, AA151267, AA156459
768040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1220 of SEQ ID NO:127, b is an integer of 15 to 1234, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.	
769956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 849 of SEQ ID NO:128, b is an integer of 15 to 863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.	R68817, R68925, R75906, H14626, H82146, H93109, H93237, N32098, N35721, N45410, N75570, W03043, W04850, AA029607, AA262861, AA463956, AA464092
770133	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1224 of SEQ ID NO:129, b is an integer of 15 to 1238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.	
770289	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 365 of SEQ ID NO:130, b is an integer of 15 to 379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.	

771964	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1772 of SEQ ID NO:131, b is an integer of 15 to 1786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.	T53984, T55243, T51230, T77632, T91326, T80819, T81219, T84909, T95454, T97320, T99226, T99269, R16575, R16634, R19765, R22987, R23096, R33095, R33188, R37437, R39255, R45185, R45185, R62594, R62642, H03891, H03892, H08679, H08680, H20556, H20650, H46154, H46155, R88298, R90733, R90759, R92224, R92332, R97325, H57663, H58503, H61709, H61913, H62747, H66685, H68924, H68954, H80053, H83342, H95786, H96135, N20464, N20472, N24026, N25491, N35235, N35419, N38769, N44900, N48399, N53146, N55089, N55095, N57767, N58580, N59732, N63942, N70290, N71759, N74938, N77300, N98411, W23555, W52690, W52160, W56557, W56635, W56598, W56594, W73408, W74230, W79843, W93916, AA031492, AA070868, AA071019, AA088788, AA100685, AA112926, AA176829, AA176851, AA193034, AA194065, AA194180, AA194579, AA194703, AA195416, AA195532, AA233792, AA233783, AA233900, AA233920, AA234128, AA234169, AA252704, AA252831, AA416743, AA418391, AA418440
772582	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:132, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.	
773387	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 620 of SEQ ID NO:133, b is an integer of 15 to 634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.	
773827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1841 of SEQ ID NO:134,	

	b is an integer of 15 to 1855, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.	
774108	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:135, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.	T96288, R31388, R32886, R63543, R63597, R75811, R75812, H20285, H20509, H20599, H21238, H24872, H29854, H29945, H41103, H41208, H44188, H44189, R85628, R91367, H83459, H83571, H97165, H97164, N25639, N29652, N29777, N32407, N32413, N32580, N32835, N41918, N42281, N56607, N57152, N57196, N69818, N70613, N93340, N93928, N94454, W24358, W25163, W30800, W37904, W37964, W40428, W68631, W68632, W70339, W80994, W81096, W81716, W81253, W81543, W81544, W94206, AA004372, AA011346, AA016002, AA028888, AA029626, AA029627, AA044028, AA044350, AA062804, AA081035, AA131270, AA131354, AA131371
774636	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:136, b is an integer of 15 to 1271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.	T54747, T69827, R14146, R50592, R55502, R73615, R73937, H41540, R84981, R85103, R87495, R88553, R88554, R88556, R88818, R88839, R89675, R91235, H51003, H51004, H51581, H79057, N70799, W02680, AA232327, AA232417, AA464467
775339	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2003 of SEQ ID NO:137, b is an integer of 15 to 2017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.	
775582	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 923 of SEQ ID NO:138, b is an integer of 15 to 937, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or	T62486, T62631, H14642, R85991, H73603, N54912, N68727, N80228, N91617, W38518, W67302, W67418, AA171395, AA214500, AA215291, AA464035

	equal to a + 14.	
775779	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2745 of SEQ ID NO:139, b is an integer of 15 to 2759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to a + 14.	
777809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1227 of SEQ ID NO:140, b is an integer of 15 to 1241, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to a + 14.	
778927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3391 of SEQ ID NO:141, b is an integer of 15 to 3405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to a + 14.	T50777, T50939, R11800, R19713, R31403, R32898, R44269, R44269, R55431, R60041, R60103, R69554, R74340, R74434, H20427, H26615, H26660, H42495, H43482, R85644, H51488, H68618, N58157, N58231, N77611, W39692, W45048, W56828, W57633, AA052900, AA057808, AA074705, AA122120, AA121079, AA121231, AA259051, AA464470
779262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2254 of SEQ ID NO:142, b is an integer of 15 to 2268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to a + 14.	R11844, R71241, R71292, H00159, H88551, H90726, H98059, N28770, N58442, N78033, W32671, AA035075, AA112651, AA112652, AA130035, AA215309, AA251209
779392	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:143, b is an integer of 15 to 1757, where both	R25284, R36255, R36256, R42970, R46635, R42970, R46635, H28773, N52867, N70541, N77890, W05403, W05783, AA085067, AA085066, AA204650, AA210753, AA211713, AA251462, AA252456, AA460350, AA460780

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.	
780149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:144, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.	
780583	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:145, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.	
780960	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:146, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.	
781469	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2664 of SEQ ID NO:147, b is an integer of 15 to 2678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.	T95791, H18820, H19074, H22604, H40723, H45802, H46056, H47074, H47156, H86819, H86886, H88675, H88724, H88972, H89058, H88972, N28987, N36053, N39668, N47281, W19145, W68543, W68544, N91577, AA044679, AA044896, AA430011
781556	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T94861, T94906, R21516, R26869, R27098, R36258, R37965, R37966, R78172, H03413, H04116, H14531, H45546, R96826, R98130, N51409, N52365, N64272, N74939, N75136,

	formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:148, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.	W23556, W35208, AA187823, AA191525, AA429367
781771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:149, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.	T95420, T99529, R50341, R52125, R72608, R72630, R72677, R72701, H26733, H26734, H30106, H59788, H82441, N75150, W42750, W42840
782033	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:150, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.	H53100, H53207, H97410, H98035, N30753, N68541, W42491, W42641, W57808, AA046603, AA046753, AA136886, AA136997, AA143419, AA143420
782105	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:151, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.	R97486, H72940, W90139
782122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1635 of SEQ ID NO:152, b is an integer of 15 to 1649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.	T54379, T60348, T61029, T54271, T57801, R10793, T78907, T78959, R49078, R55635, R67844, R67845, R69587, R72600, R72666, H04742, H04830, H16978, H24654, H26129, H26308, H26395, H26467, H28100, H28205, H28252, H28895, H28896, H30485, H39554, H42595, H42603, H42662, H43740, H44345, H44346, H44546, H44547, H44960, H45012, H45860, R88120, R88214, H51204, H58080, H58081, H64553, H64654, H70033, H70034, H86451, H70034, H99833, N24525, N29867, N30752, N35500, N39259, N42463, N44804,

		N52550, N53985, N57289, N58726, N63349, N67624, N67663, N68157, N70299, N80615, N93230, N94595, N98489, W19633, W23803, W25087, W31034, W37981, W37982, W42579, W44389, W49677, W57614, W57871, W58142, W67781, W67840, W68147, W68474, W68699, W68791, W69717, W80749, W80837, N89879, AA025233, AA025568, AA025686, AA026020, AA033846, AA039625, AA039693, AA046842, AA047013, AA057608, AA057676, AA064637, AA064680, AA074448, AA083591, AA098837, AA102142, AA113374, AA113402, AA115525, AA114948, AA128972, AA128973, AA133142, AA146949, AA148086, AA149283, AA149377, AA160012, AA160688, AA172144, AA180932, AA182561
783135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 646 of SEQ ID NO:153, b is an integer of 15 to 660, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.	
783245	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:154, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.	
783247	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:155, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.	AA155638
783413	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H58751, H93683, H93684, N93167, W19186, W19958, W38771, N91367

	sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:156, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.	
784407	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1113 of SEQ ID NO:157, b is an integer of 15 to 1127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.	
784548	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:158, b is an integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.	
785075	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1491 of SEQ ID NO:159, b is an integer of 15 to 1505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.	
785677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 722 of SEQ ID NO:160, b is an integer of 15 to 736, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.	

786238	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 981 of SEQ ID NO:161, b is an integer of 15 to 995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.	
786389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:162, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.	
786929	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:163, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.	
786932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:164, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.	
787078	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1101 of SEQ ID NO:165, b is an integer of 15 to 1115, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.	
787139	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:166, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.	
787283	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:167, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.	R22724
788761	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:168, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.	
788988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 760 of SEQ ID NO:169, b is an integer of 15 to 774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.	
789092	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	AA234588

	between 1 to 388 of SEQ ID NO:170, b is an integer of 15 to 402, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.	
789298	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 782 of SEQ ID NO:171, b is an integer of 15 to 796, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.	
789299	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:172, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.	
789718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:173, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to a + 14.	
789957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1877 of SEQ ID NO:174, b is an integer of 15 to 1891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.	T51260, T61941, T62167, T77034, T90753, R38108, N32708, N92379, W24621, W42543, W42478, AA128007, AA128031, AA134234, AA424998
789977	Preferably excluded from the present invention are one or more	T56442, T78292, R37940, R56008, R56009, R56573, R56574, H11080, N34431, N48665,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2147 of SEQ ID NO:175, b is an integer of 15 to 2161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.	AA010749, AA011177, AA070806, AA070882, AA146859, AA147636, AA147691, AA164223, AA164224, AA210729, AA210859, AA243063, AA243070, AA464493, AA464494
790285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2397 of SEQ ID NO:176, b is an integer of 15 to 2411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.	T66279, T66328, T84164, T85098, R24232, R24233, H03657, H03658, H98526, H98556, H99618, N22728, N29400, N32172, N33953, N41460, N69471, N70552, N73722, W03893, W44579, W72407, W76486, W78102, W79410, N90963, AA044816, AA044841, AA086039, AA086121, AA088877, AA102298, AA130887, AA131529, AA131603, AA181784, AA182515, AA190450, AA191392, AA223757
790509	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1324 of SEQ ID NO:177, b is an integer of 15 to 1338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.	T68040, H17760, AA101036, AA129837
790775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1600 of SEQ ID NO:178, b is an integer of 15 to 1614, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.	N25320, N31432, W81044, W81097
790888	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4278 of SEQ ID NO:179, b is an integer of 15 to 4292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or	R14550, R15204, T26493, R21597, R22908, R23010, R41211, R41649, R43371, R41211, R41649, R43371, R58989, R59048, H05739, H05845, H17266, H17265, H23579, H44104, H46505, H47043, H58955, H59002, H73676, H73730, H80078, H82275, H82289, H82399, H82381, H97810, H98133, H98737, N23117, N24310, N25196, N25265, N27792, N28735, N29893, N33395, N33904, N36066, N36839, N42542, N46060, N51230, N59535, N67737,

	equal to a + 14.	N73641, N78481, N78694, W03555, W15202, W52445, W52723, W95124, AA047257, AA057142, AA204699, AA251464, AA430598
791506	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 229 of SEQ ID NO:180, b is an integer of 15 to 243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to a + 14.	
791649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 799 of SEQ ID NO:181, b is an integer of 15 to 813, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to a + 14.	
791802	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:182, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to a + 14.	
792002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1081 of SEQ ID NO:183, b is an integer of 15 to 1095, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to a + 14.	T49735, T49736, T95310, T95391, T99384, T99612, R63493, R63494, H27739, R91698, R92136, H52608, H57619, H58464, H61415, H62139, H69019, H87167, H87669, N21358, N70307, N79596, W19063, W58498, W58651, W79687, W81289, AA099849, AA099972, AA232767
792291	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	T55436, R21797, R22403, R22452, R22916, R23020, R76901, R77068, H22573, H25752, H25866, R83900, H50717, H50821, H64026, H64791, H95702, N64545, N69769, N74704, N80341, W05092, W79489, W79634,

	between 1 to 3661 of SEQ ID NO:184, b is an integer of 15 to 3675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.	AA005055, AA005007, AA025043, AA036711, AA037127, AA043916, AA055100, AA063627, AA069142, AA069230, AA069323, AA069376, AA112277, AA112531, AA115279, AA151238, AA151239, AA151582, AA149398, AA149961, AA150069, AA158029, AA158321, AA158692, AA158693, AA161232, AA236787, AA236834, AA256776, AA261961
792371	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1026 of SEQ ID NO:185, b is an integer of 15 to 1040, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.	
792660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:186, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.	T59054, T86590, T83271, R48677, R53483, R53482, R62329, R62330, R66651, R67372, R69095, R69210, R71144, R82632, R82676, H15764, H15765, H19518, H19605, H27898, H42872, H42936, H49329, H49330, H50062, H50061, H87268, H87324, H96667, N22675, N92574, W37223, W37563, W38866, W61119, W65380, AA035095, AA035635, AA037254, AA054951, AA062973, AA082301, AA132472
792782	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of SEQ ID NO:187, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.	
792890	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1272 of SEQ ID NO:188, b is an integer of 15 to 1286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.	AA251351

792931	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1724 of SEQ ID NO:189, b is an integer of 15 to 1738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.	
792943	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:190, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.	
793104	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 236 of SEQ ID NO:191, b is an integer of 15 to 250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.	
793445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1888 of SEQ ID NO:192, b is an integer of 15 to 1902, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.	AA034998, AA044249, AA088830, AA429418
793446	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 546 of SEQ ID NO:193, b is an integer of 15 to 560, where both a and b correspond to the positions of	T57765, T60664, H01264, H45774, H54790, H54842, H64484, H64485, N98810, W58332, W58653, W74582, W79320, W79420, W79565, W92452, AA027210, AA027209, AA029725, AA029663, AA088693, AA121506, AA127731, AA428362

	nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.	
793639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:194, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14.	N69881, N93023, N98853, W21375, W73944, W77988, AA169530, AA169837, AA176453, AA176931
794213	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:195, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.	N53897, N55318
795858	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1758 of SEQ ID NO:196, b is an integer of 15 to 1772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.	
795955	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:197, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.	
796359	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 543 of SEQ ID NO:198, b is an integer of 15 to 557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.	
796555	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2597 of SEQ ID NO:199, b is an integer of 15 to 2611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.	T69136, T69194, T95612, T95713, R53091, R73126, N41876, N49174, W05348, W04725, W31397, W31827, W92674, AA039513
796675	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2302 of SEQ ID NO:200, b is an integer of 15 to 2316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.	
796743	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1133 of SEQ ID NO:201, b is an integer of 15 to 1147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.	
796792	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 674 of SEQ ID NO:202, b is an integer of 15 to 688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.	
799668	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 290 of SEQ ID NO:203, b is an integer of 15 to 304, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.	
799669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:204, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.	
799673	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 537 of SEQ ID NO:205, b is an integer of 15 to 551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.	
799674	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:206, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.	
799678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:207, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or	

	equal to a + 14.	
799728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 255 of SEQ ID NO:208, b is an integer of 15 to 269, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to a + 14.	
799748	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:209, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to a + 14.	H19497, H19579, H50117, H50164, H52826, H52827, H61184, H62087, H96290, H96291, N20586, N21261, N28978, N30137, N30490, N35750, W31933, W37535, N90542, AA418545, AA418511
799760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:210, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to a + 14.	
799805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 190 of SEQ ID NO:211, b is an integer of 15 to 204, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where b is greater than or equal to a + 14.	
800296	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:212, b is an integer of 15 to 1271, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.	
800327	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1011 of SEQ ID NO:213, b is an integer of 15 to 1025, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.	
800816	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 337 of SEQ ID NO:214, b is an integer of 15 to 351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.	
800835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1073 of SEQ ID NO:215, b is an integer of 15 to 1087, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.	
805429	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1963 of SEQ ID NO:216, b is an integer of 15 to 1977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.	
805458	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T82438, T82439, R19121, R20391, R28602, R36743, R43508, R46035, R43508, R46035, R79588, H24625, N28372, N28785, N29421, N35476, N57353, N72836, N79096, W03034,

	formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:217, b is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.	AA016073, AA019733, AA021030, AA062895, AA081968, AA115692, AA133511, AA151852, AA149707, AA194903, AA194902
805478	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1631 of SEQ ID NO:218, b is an integer of 15 to 1645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14.	
805805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:219, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14.	
806486	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:220, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14.	
806498	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:221, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14.	
806819	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:222, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14.	
810870	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:223, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14.	R50267, R50730, H27672, H27673, H30138, H99256, N74342, N80868, W05054, W07601
811730	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:224, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14.	
813025	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:225, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14.	
813233	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:226, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:226, and where b is greater than or equal to a + 14.	
813262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2363 of SEQ ID NO:227, b is an integer of 15 to 2377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to a + 14.	
815637	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 449 of SEQ ID NO:228, b is an integer of 15 to 463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to a + 14.	
815853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1218 of SEQ ID NO:229, b is an integer of 15 to 1232, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:229, and where b is greater than or equal to a + 14.	R53293, R59708, R59818, R88929, R89609, H78819, N52182, AA125808, AA128281
815999	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:230, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to a + 14.	
823427	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:231,	T53986, T60846, T72425, R18752, H22479, H50211, N40817, N93431, W21474, W21308, W32281, W44860, W95821, N90881, AA132037, AA131965, AA151157, AA155868, AA156600, AA156837, AA157061, AA157045, AA160623, AA169460, AA176447, AA178894,

	b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14.	AA179764, AA180438, AA181145, AA181144, AA196382, AA196478
823704	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1460 of SEQ ID NO:232, b is an integer of 15 to 1474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14.	
824798	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1768 of SEQ ID NO:233, b is an integer of 15 to 1782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14.	
825018	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2194 of SEQ ID NO:234, b is an integer of 15 to 2208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14.	
825076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2566 of SEQ ID NO:235, b is an integer of 15 to 2580, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14.	
825787	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 2994 of SEQ ID NO:236, b is an integer of 15 to 3008, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14.	
826116	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 863 of SEQ ID NO:237, b is an integer of 15 to 877, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14.	
826147	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3025 of SEQ ID NO:238, b is an integer of 15 to 3039, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to a + 14.	
827020	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:239, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to a + 14.	
827586	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 483 of SEQ ID NO:240, b is an integer of 15 to 497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to a + 14.	

827732	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 302 of SEQ ID NO:241, b is an integer of 15 to 316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to a + 14.	
827735	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 815 of SEQ ID NO:242, b is an integer of 15 to 829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to a + 14.	
827740	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:243, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to a + 14.	R21513, R22316, R42033, R43706, R42033, R43706, R63113, R70954, R71006, N48618, N53377, AA912400
827808	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2839 of SEQ ID NO:244, b is an integer of 15 to 2853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14.	
828251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1183 of SEQ ID NO:245, b is an integer of 15 to 1197, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14.	
828357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 834 of SEQ ID NO:246, b is an integer of 15 to 848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14.	
828449	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:247, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14.	
828612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:248, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14.	R28513, R28661, R31336, R41867, R41867, R60004, H19945, H19946, H22061, H46271, H46342, H82619, H82618, N20678, W96169, AA010842, AA278855, AA582295, AA583721, AA639735, AA579409, AA568321, AA833752, AA907437, AI054389, W22584
828647	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2411 of SEQ ID NO:249, b is an integer of 15 to 2425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14.	
828698	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 1394 of SEQ ID NO:250, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14.	
828962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 480 of SEQ ID NO:251, b is an integer of 15 to 494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14.	
828982	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2477 of SEQ ID NO:252, b is an integer of 15 to 2491, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14.	T64550, T65973, T94849, T94894, R07359, R07409, R34782, R35670, R35781, R56137, R56532, R64039, R66397, R67131, H01215, H02256, H02354, H03227, H04019, R94572, R94573, H51242, H60286, H65939, H72416, H72857, N22537, N24628, N24936, N33813, N35712, N35830, N35916, N43982, N51363, N64462, N70838, N75470, N75760, W01444, W05279, W57605, W58752, W72612, W72970, W73260, W73535, W76678, W76207, W94918, W91971, W92319, W92355, AA024690, AA024643, AA028083, AA028084, AA028169, AA035743, AA045830, AA045917, AA081723, AA086310, AA085740, AA102651, AA101305, AA126788, AA126837, AA126865, AA127295, AA129688, AA129664, AA133503, AA133504, AA132801, AA134537, AA134547, AA186712, AA188264, AA215597, AA463977, AA464112, AA417286, AA417312, AA259228, AA279952, AA287814, AA468227, AA468302, AA526480, AA553703, AA587072, AA635683, AA639361, AA573471, AA579754, AA579812, AA580600, AA730425, AA741436, AA804629, AA829189, AA830255, AA865594, AA885821, AA918979, AA962033, AA985542, AA985571, AA987607, AA995783, AI075334, D79160, N84712, N88655, C03235, AA094028
829282	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:253, b is an integer of 15 to 1125, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14.	
829368	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:254, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14.	R61547, R76124, H01565, H02950, H04248, H29996, H99672, W19970
829751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:255, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14.	
829773	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:256, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14.	T96982, T97094, H53488, H53861, H64894, H65486, N62304, N67480, N78709, W03409, W07598, W73770, AA025496, AA025812, AA133948
829934	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2390 of SEQ ID NO:257, b is an integer of 15 to 2404, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14.	
829942	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	T64541, T65964, R01423, R01424, R05277, R19450, R44699, R51779, R51780, R44699, H11322, H11349, H13859, H13911, H21393, H21437, H21890, H22117, H45982, H46047, H47137, R98886, H54491, H54854, H98744,

	between 1 to 2078 of SEQ ID NO:258, b is an integer of 15 to 2092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14.	N23465, N37080, N46155, N46396, N58995, N62715, N93640, W60228, W60227, W74349, W76544, W87768, W87883, W90517, W90518, AA010775, AA011055, AA029083, AA029084, AA036822, AA057660, AA075916, AA082814, AA101057, AA130702, AA132788, AA133063, AA147813, AA148063, AA151487, AA151511, AA173298, AA173348, AA181036, AA187993, AA187994, AA192370, AA192357, AA243010, AA243264, AA250948
829951	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 373 of SEQ ID NO:259, b is an integer of 15 to 387, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14.	
830173	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3698 of SEQ ID NO:260, b is an integer of 15 to 3712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14.	T52493, T52572, T56913, T61268, T61320, T70063, T70130, T72005, T87844, T94182, T70248, R24534, R24639, R31200, R64161, R64274, R70751, R70750, H16189, H89274, H99749, N25430, N25537, N32578, N32816, N34120, N34134, N34491, N35081, N42260, N43821, N62152, N62798, N64065, N64169, N67362, N69808, N74678, N93912, N49165, W04704, W05040, W16565, W19920, W31806, W31907, W37354, W37355, W40493, W45266, W45455, W52925, W58628, W92222, W92345, N91265, AA027083, AA027124, AA028969, AA029137, AA029257, AA083657, AA084297, AA121151, AA121131, AA126957, AA127166, AA128353, AA128495, AA128834, AA132690, AA132783, AA136553, AA152414, AA150706, AA150808, AA156272, AA164766, AA164767, AA171427, AA171794, AA173592, AA173949, AA190421, AA190580, AA191383, AA224415, AA232135
830200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 883 of SEQ ID NO:261, b is an integer of 15 to 897, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:261, and where b is greater than or equal to a + 14.	AA524284, AA662477, AA887924

830365	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1891 of SEQ ID NO:262, b is an integer of 15 to 1905, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14.	R42905, R59718, R62419, R72182, R72228, H22520, H22519, H25889, H45643, H46451, H46992, H84483, N50834, N92573, AA022699, AA022791, AA037734, AA037735, AA040585, AA040557, AA047816, AA159187, AA159282, AA223337, AA505391, AA515591, AA524466, AA613383, AA627298, AA578816, AA769153, AA826456, AA830896, AA831083, AA837917, AA977053, AI083822, AI090301, AI084104
830456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1410 of SEQ ID NO:263, b is an integer of 15 to 1424, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14.	T39800, T39875, T40331, T80148, R01135, R05754, R12866, R15287, R21703, R39361, H00652, H00741, H05366, H17706, H23423, R97800, R97849, N25478, N41797, N48511, N98906, W19893, W23945, W35174, W60540, W78229, W79282, W84685, AA022952, AA026821, AA026953, AA074956, AA075111, AA114974, AA114988, AA192860, AA193064
830549	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1273 of SEQ ID NO:264, b is an integer of 15 to 1287, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14.	R60171, H26796, H96303, N91699, W25137, AA069218, AA088565, AA161178
830602	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 977 of SEQ ID NO:265, b is an integer of 15 to 991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14.	
830610	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2306 of SEQ ID NO:266, b is an integer of 15 to 2320, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14.	
830644	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:267, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14.	
830707	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1832 of SEQ ID NO:268, b is an integer of 15 to 1846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14.	
830709	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:269, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14.	
830733	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 866 of SEQ ID NO:270, b is an integer of 15 to 880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14.	T26638, R49962, H96664, N71762, N90691, AA040156, AA128271, AA418045, AA418216, AA535799, AA583405, AA768811
830768	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2470 of SEQ ID NO:271, b is an integer of 15 to 2484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14.	
830855	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:272, b is an integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14.	H17127, AA100311, AA112910, AA282249, AA578649, AA748590
830949	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3295 of SEQ ID NO:273, b is an integer of 15 to 3309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14.	
830965	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:274, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14.	
830973	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2014 of SEQ ID NO:275, b is an integer of 15 to 2028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14.	
830979	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1441 of SEQ ID NO:276, b is an integer of 15 to 1455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14.	
830989	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:277, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14.	
831134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:278, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14.	
831200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:279, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14.	
831260	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1178 of SEQ ID NO:280, b is an integer of 15 to 1192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or	R15008, R28066, R68324, H20638, N25438, N67982, N67983, N67999, N68004, N68005, N80403, N80423, N80429, N80430, AA024581, AA024582, AA024637, AA862760, AA091142

	equal to a + 14.	
831531	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:281, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to a + 14.	T66624, R16038, R26139, R26353, H15795, H16285, H21749, H21945, H22698, H23978, H52286, H52523, H60184, H60227, H68044, H81748, H81749, N46859, N47179, N51722, N51808, AA031701, AA031866, AA043760, AA043761, AA081005, AA081148, AA195519, AA470636, AA534463, AA555198, AA631348, AA721036, AA737025, AA761301, AA764993, AA765314, AA765749, AA878422, U47720, C21223
831665	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1079 of SEQ ID NO:282, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to a + 14.	
831724	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1542 of SEQ ID NO:283, b is an integer of 15 to 1556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to a + 14.	R52161, N45179, N68350, N94021, W02782, W24840, W61323, AA907441
831884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:284, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to a + 14.	
831897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1569 of SEQ ID NO:285, b is an integer of 15 to 1583, where both	AA056348, AA127534

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14.	
831922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:286, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14.	
831963	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:287, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14.	
832074	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:288, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14.	
832266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1020 of SEQ ID NO:289, b is an integer of 15 to 1034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14.	T70612, T70879, H13555, H23264, R97792, R97842, N75850, W07434, W19866, N90056, AA043395, AA463232, AA463231
832309	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 3077 of SEQ ID NO:290, b is an integer of 15 to 3091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14.	
832342	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 504 of SEQ ID NO:291, b is an integer of 15 to 518, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14.	
832351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 484 of SEQ ID NO:292, b is an integer of 15 to 498, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14.	
832352	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 455 of SEQ ID NO:293, b is an integer of 15 to 469, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14.	
832434	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 654 of SEQ ID NO:294, b is an integer of 15 to 668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14.	
832490	Preferably excluded from the present	T86496, H24346, R84505, N26874, N98621,

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1386 of SEQ ID NO:295, b is an integer of 15 to 1400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14.	W04678, W04692, W24267, W93387, W94971, AA036953, AA136869, AA136799, AA147214, AA160413, AA535592, AA931261, AA931403, AA962726, AA992456
832573	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:296, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14.	
832580	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:297, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14.	
833394	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 878 of SEQ ID NO:298, b is an integer of 15 to 892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14.	
835355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:299, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	AA076638, AA916592, AI088936, AI089690

	NO:299, and where b is greater than or equal to a + 14.	
835497	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1955 of SEQ ID NO:300, b is an integer of 15 to 1969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14.	
835728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:301, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14.	
835978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2790 of SEQ ID NO:302, b is an integer of 15 to 2804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is greater than or equal to a + 14.	
836091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3845 of SEQ ID NO:303, b is an integer of 15 to 3859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to a + 14.	R02093, R02205, R02336, R02439, R19436, R44685, R44685, R72354, H10160, H49884, H49885, N23208, N28789, N29901, N42953, N55093, N77305, N99373, W46396, W46504, AA082311, AA176281, AA176282, AA227971, AA228079, AA234964, AA234145, AA281787, AA281656, AA524468, AA551888, AA631173, AA639499, AA811344, AA830439, AA831974, AA923665, C03439, AA641655, AA091346, AA400968, AA400884
836274	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3364 of SEQ ID NO:304,	T75442, R20393, R43511, R43511, R73650, R73731, R80152, R80886, H97932, H98616, N33018, N71679, N99650, AA001053, AA001089, AA044947, AA044943, AA149057, AA464856, AA427892, AA228265, AA230021, AA482694, AA483691, AA484850, AA513037,

	b is an integer of 15 to 3378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to a + 14.	AA516076, AA532381, AA583355, AA618566, AA577028, AA730651, AA730790, AA745667, AA829807, AA923038, AA931937, AA932867, AA934400, AA934413, AA971551, AA971743, AA972772, AA977253, AA992454, AA994794, AI089906, AI094921, D79281, C06099, D44840, C20741, AA283186, AA292346, AA394164
836731	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1000 of SEQ ID NO:305, b is an integer of 15 to 1014, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to a + 14.	
838014	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:306, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to a + 14.	
838874	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 652 of SEQ ID NO:307, b is an integer of 15 to 666, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14.	R61165, N44200
839120	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:308, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14.	T74462, R18264, H23432, AA279685, AA847441, AA904076, AA393782

839611	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6149 of SEQ ID NO:309, b is an integer of 15 to 6163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14.	T93695, T93696, T96161, R32227, R32254, R32304, R33503, R34044, R71178, H93366, N50709, N55039, AA165143, AA199856, AA199927, AA234331, AA262892, AA423987, AA423986, AA525886, AA661602, AA731504, AA741228, AA814795, AA828858, AA829196, AA831198, AA834822, AA865590, AA886436, AA903649, D82270, D82453, D82464, AA642466, AA219620, AA219628, AA400707, AA400674, AA421941, AA633988, AA663219, AA663250, AA665538, AA724260, AI074714, T26891, T26926
840138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:310, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14.	
840616	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2149 of SEQ ID NO:311, b is an integer of 15 to 2163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14.	
840780	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1383 of SEQ ID NO:312, b is an integer of 15 to 1397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is greater than or equal to a + 14.	
840857	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4092 of SEQ ID NO:313, b is an integer of 15 to 4106, where both	T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, N58504, N78093, N92665, N99611, AA005068, AA007333, AA007334, AA036884, AA044715, AA045458, AA046500, AA045654, AA115936, AA121004,

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to a + 14.	AA126775, AA133605, AA133606, AA133980, AA181633, AA182611, AA232979, AA233365, AA459953, AA460042, AA282826, AA285050, AA506082, AA558006, AA601060, AA767799, AA804323, AA807029, AA807087, AA825536, AA833810, AA922732, AA928638, AA960990, N56482, N62047, W27456, W26569, AA092778, AA652535, AA065256, AA065257, AA450197, AA452846, AA452986, AA705224, Z19460, AA884767, AA969488, AA977494, AI002996, AI032008, Z28526, D20112, T19336
840862	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:314, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to a + 14.	T94528, N40545, N46592, N92934, AA570273, AA873604, AA910827, AA932397, AA971868, AI095210, N56229, AA648290, F20835, AA629912
840864	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1924 of SEQ ID NO:315, b is an integer of 15 to 1938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to a + 14.	R40870, R44820, H26640, W78814, W80713, AA195492, AA937549, AI085492, AI094865, AA449317, AA884600, AA909529, AA923452, AA971781, AI084795, AI089007, AA702758, AA702769
840936	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:316, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to a + 14.	
840938	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:317, b is an integer of 15 to 837, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to a + 14.	
841884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1434 of SEQ ID NO:318, b is an integer of 15 to 1448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to a + 14.	
842241	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1479 of SEQ ID NO:319, b is an integer of 15 to 1493, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to a + 14.	
843712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 595 of SEQ ID NO:320, b is an integer of 15 to 609, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14.	R02291, N94598, W85882, AA255975
844040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 488 of SEQ ID NO:321, b is an integer of 15 to 502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14.	W24428, AA143434, AA459809
844336	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2616 of SEQ ID NO:322, b is an integer of 15 to 2630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14.	
844612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1860 of SEQ ID NO:323, b is an integer of 15 to 1874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14.	
844617	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2311 of SEQ ID NO:324, b is an integer of 15 to 2325, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14.	
845251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:325, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14.	T68474, AA159183, AA464447, AA424290, AA424487, AA631793, AA928390, AA946921, AA975194, AA977141, AA430527, AA430612, AA477798
845764	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 230 of SEQ ID NO:326, b is an integer of 15 to 244, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14.	
846187	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2440 of SEQ ID NO:327, b is an integer of 15 to 2454, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14.	

Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

The present invention also encompasses variants of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the

nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table 1, an ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of

the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases

were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the

purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that

"[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed

herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a deposited library, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells,

Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30

amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a depostied cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that

include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700,701- 750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from

about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700,701- 750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context "about" includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region.

Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, 1441-1460, 1461-1480, 1481-1500, 1501-1520, 1521-1540, 1541-1560, 1561-1580, 1581-1600, 1601-1620, 1621-1640, 1641-1660, 1661-1680, 1681-1700, 1701-1720, 1721-1740, 1741-1760, 1761-1780, 1781-1800, 1801-1820, 1821-1840, 1841-1860, 1861-1880, 1881-1900, 1901-1920, 1921-1940, 1941-1960, 1961-1980, and 1981 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed

herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table 1). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Table 4

Sequence/ Contig ID	Epitope
508678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 422 as residues: Gln-21 to Arg-43.
508968	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 423 as residues: Thr-1 to Lys-6.
509029	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 424 as residues: Asp-1 to Trp-8, Thr-12 to Cys-19, Pro-41 to Leu-51.
522632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 426 as residues: Cys-69 to Asn-74, Lys-83 to Gly-89.
524655	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 427 as residues: Tyr-28 to Asn-35, Ile-45 to Lys-55.
525847	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 428 as residues: Lys-27 to Asp-33.
530306	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 429 as residues: Arg-1 to Arg-11, Tyr-21 to His-27.
532818	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 430 as residues: Pro-10 to Thr-21, Asp-32 to Thr-38, Gly-47 to Glu-60.
533385	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 431 as residues: Asn-17 to Trp-22, Pro-34 to Glu-49, His-61 to Ser-71.
533532	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 432 as residues: Glu-29 to Lys-37, Lys-110 to Ile-118, Arg-126 to Cys-135, Lys-157 to Gly-163, Gln-188 to Trp-201, Glu-269 to Thr-278.
534852	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 433 as residues: Gln-1 to Ser-14, Thr-23 to Val-31, Cys-43 to Ala-56, Glu-58 to Ser-96, Gly-101 to Tyr-109, Asn-143 to Tyr-148, Pro-154 to His-164, Ser-195 to Asn-201, Pro-264 to Pro-271.
537910	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 434 as residues: Pro-4 to Ala-11, Pro-110 to Arg-122.
539577	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 436 as residues: Pro-9 to Gln-19.
548595	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 439 as residues: Asp-27 to Asp-33, His-54 to Tyr-59, Ile-91 to Pro-96.
549337	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 440 as residues: Pro-38 to Asp-43, Arg-155 to Phe-162, Pro-164 to Asp-170, Pro-172 to Gly-182.
553091	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 442 as residues: Lys-55 to Lys-62, Gln-67 to Val-76, Lys-101 to Glu-111, Lys-125 to Arg-140, Arg-161 to Arg-166, Gln-171 to Asp-187.
553827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 443 as residues: Glu-17 to Pro-22, Pro-70 to His-76, Thr-84 to Arg-92, Asp-109 to Tyr-117.
556350	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 444 as residues: Glu-1 to Ser-15, Phe-17 to Pro-22, Lys-116 to Arg-131.
556351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 445 as residues: Gln-9 to Phe-23, Cys-53 to Ser-64, Glu-86 to Asp-93, Ile-100 to Glu-112, Tyr-124 to Glu-133, Ser-197 to Ser-204, Asn-208 to Glu-214, Lys-228 to Lys-233, Tyr-248 to Lys-259, Pro-330 to Ala-335, Gln-349 to Lys-355, Ala-365 to Glu-374, Ser-376 to Ser-397.
557007	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 446 as residues: Pro-46 to Tyr-54, Pro-81 to Gly-87, Pro-97 to Gly-104, Leu-106 to Asn-116, Asn-129 to Phe-134, Lys-147 to Tyr-158, Ala-192 to Ser-199, Asp-204 to Glu-215, Gly-221 to Ser-232.
558456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 448 as

	residues: Glu-19 to Tyr-24, Ser-60 to Thr-65, Thr-82 to Pro-88.
558708	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 449 as residues: Arg-13 to Ala-20, Pro-27 to Arg-32, Lys-37 to Glu-62.
574789	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 450 as residues: Gly-16 to Lys-21.
578203	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 451 as residues: Thr-7 to Arg-18.
588869	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 453 as residues: Pro-14 to Ser-19, Glu-55 to Phe-60, Asp-93 to Ser-98, Thr-138 to Tyr-144, Asn-155 to Phe-163, Arg-168 to Ser-175, Gln-205 to Lys-210, Phe-226 to Thr-233.
597076	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 454 as residues: Ser-50 to Gln-56.
598656	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 455 as residues: Ser-85 to Tyr-92, Arg-109 to Lys-114.
614329	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 457 as residues: Arg-59 to Ala-67, Asn-78 to Arg-85.
620956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 459 as residues: Ala-11 to Gln-16.
621889	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 460 as residues: Ser-84 to Gly-99, Pro-101 to Ser-112.
651784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 462 as residues: Gly-29 to Gly-35, Ala-37 to Ala-48.
651826	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 463 as residues: Arg-1 to Ser-16, Gln-49 to Lys-60, Glu-77 to Leu-83, Gln-91 to Arg-100, Phe-140 to Ala-154, Asp-214 to Leu-219, Ala-258 to Met-275, Ile-289 to Lys-295, Ala-314 to Glu-320, Arg-327 to Met-332, Thr-383 to Ser-388, Ser-425 to Asp-433.
653282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 464 as residues: Arg-12 to Ile-19, Glu-23 to Pro-29, Pro-37 to Val-45.
657122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 465 as residues: Ala-6 to Gly-13, Arg-41 to Thr-47.
661442	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 466 as residues: Arg-6 to Ser-11, Asp-53 to Ser-59, Ala-88 to Ala-104, Thr-114 to Asn-121, Glu-128 to Val-137, Asn-144 to Thr-150, Ser-174 to Asn-180, Gly-203 to Asp-212.
664914	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 467 as residues: Pro-12 to Lys-17.
666654	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 468 as residues: Thr-5 to Leu-10, Pro-13 to Leu-24.
667084	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 469 as residues: Pro-1 to Pro-9, Gly-50 to Ser-55, Gly-80 to Ser-85, Gly-91 to Tyr-96, Arg-144 to Gln-160, Asp-195 to Thr-202, Lys-246 to Glu-252, Met-283 to Glu-288, Glu-292 to Glu-299, Ser-304 to Asn-310, Ala-356 to Tyr-362, Met-387 to Tyr-394, Gln-424 to Thr-431, Ser-450 to Arg-459.
667380	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 470 as residues: Pro-1 to Pro-6, Thr-134 to Gln-140, Tyr-142 to Arg-150.
671315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 472 as residues: Ala-16 to Gly-21, Glu-28 to Gly-35.
671993	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 473 as residues: Pro-8 to Ser-23.
674618	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 474 as residues: Ile-3 to Ser-11, Arg-24 to Glu-30.
675027	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 475 as residues: His-47 to Ile-52, Ala-71 to Arg-76, Asp-78 to Lys-87.
677202	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 476 as residues: Val-45 to Gly-50, Thr-56 to Glu-64.
678504	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 477 as residues: Arg-7 to Ser-19.

678985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 478 as residues: Lys-17 to Thr-23, Leu-26 to His-36, His-41 to Pro-56, Ala-60 to Gly-71, Lys-77 to Ser-91, Asp-101 to Lys-109, Asp-200 to Gly-206, Asp-245 to Leu-253, Gln-262 to Phe-274.
682161	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 479 as residues: Arg-5 to Pro-11, Pro-22 to Thr-29, Trp-53 to Arg-62, Pro-69 to Gly-78, Lys-98 to Tyr-103, Glu-144 to His-151, Pro-172 to Leu-178, Gln-193 to Glu-200.
683476	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 480 as residues: Ala-5 to Trp-19.
693589	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 482 as residues: Cys-1 to Arg-13, Pro-15 to Gly-21, Gly-54 to Ser-59, Trp-73 to Lys-78, Ser-90 to Arg-104.
694991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 483 as residues: Lys-1 to Thr-6, Pro-8 to Gly-19, Val-61 to Arg-66.
698669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 485 as residues: Pro-31 to His-36, Gly-43 to Tyr-48, Glu-136 to Ser-142, Pro-178 to Arg-183, Pro-273 to Asp-278, Gly-318 to Cys-326.
707357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 488 as residues: Gly-6 to Arg-21, Arg-89 to Asp-94.
707360	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 489 as residues: Ser-13 to Glu-26, Ser-48 to Val-55, Lys-85 to Thr-91, Asp-115 to Trp-120.
707375	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 490 as residues: Arg-1 to Gly-6, Ala-12 to Arg-19, Arg-34 to Arg-40, Arg-47 to Ala-58, Ser-67 to Thr-80, Ser-109 to Ser-117, Asn-134 to Ser-141, Pro-175 to Arg-181, Lys-212 to Thr-218, Asp-275 to Cys-285.
707754	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 491 as residues: Val-32 to Leu-41, Asn-55 to Arg-63, Pro-104 to Ala-113.
712248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 493 as residues: Ser-13 to Gly-20, Gln-36 to Ser-41, Pro-44 to Phe-58.
715445	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 494 as residues: Gly-23 to Thr-29, Ser-32 to Val-40, Lys-181 to Ser-188, Glu-197 to Gln-204, Arg-244 to His-249, Ala-253 to Thr-264.
716362	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 495 as residues: Cys-1 to Gly-8, Arg-71 to Ser-77, His-102 to Ser-108.
716835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 496 as residues: Gln-7 to Glu-14, Ala-24 to Arg-41.
717685	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 498 as residues: Gly-1 to Ala-7, His-70 to Gly-76, Gln-130 to Thr-135, Thr-182 to Pro-189, Asn-259 to Leu-267, Glu-280 to Ala-289, Gln-303 to Asn-310.
719755	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 499 as residues: Asp-14 to Pro-25, Pro-59 to Glu-100, Cys-126 to Gly-145, Pro-158 to Lys-164, Lys-176 to Leu-197, Leu-221 to Tyr-238.
720389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 500 as residues: Thr-13 to Ala-19, Ala-26 to Pro-36, Ser-63 to Gly-68.
720903	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 501 as residues: Asn-6 to Ser-11, Ala-91 to Arg-99, Trp-107 to Tyr-113, Tyr-131 to Met-137, Asp-150 to Val-157.
721562	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 503 as residues: Asp-39 to Ile-45.
722775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 504 as residues: Pro-34 to Ser-41, Cys-49 to Arg-55, Thr-92 to Ala-98, Thr-160 to Gly-173, Thr-194 to Pro-200, Gly-274 to Trp-282, Pro-285 to Ala-291.
724463	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 505 as residues: Glu-9 to Lys-15, Pro-23 to Tyr-33.
728418	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 507 as residues: Ala-6 to Gln-11, Ser-25 to Ser-30, Lys-63 to Gly-69, Ser-108 to Asp-118, Arg-

	127 to His-132, Asp-156 to Cys-161.
728920	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 508 as residues: Thr-7 to Ala-15.
732958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 509 as residues: Thr-10 to Ala-15, Pro-63 to Ser-78, Ser-82 to Leu-94.
733134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 510 as residues: Arg-4 to Gly-24, Lys-47 to Phe-55, Lys-61 to Ala-67, Gly-108 to Thr-114, Pro-184 to Pro-191, Pro-292 to Arg-299, Pro-355 to Glu-392.
734099	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 511 as residues: His-1 to Arg-7, Gln-15 to Ala-23, Met-43 to Gln-55.
738911	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 515 as residues: Arg-4 to Asp-10, Ser-64 to His-75, Pro-127 to Asn-136, Phe-143 to Gln-150.
739226	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 516 as residues: Asn-1 to Thr-7.
739527	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 517 as residues: Gly-1 to Arg-9, Val-28 to Gly-39, Asp-52 to Leu-60, Ala-106 to Trp-117.
744331	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 520 as residues: Ser-17 to Arg-24.
744751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 521 as residues: Ser-8 to Val-13, Pro-34 to Cys-40, Tyr-48 to Ser-55, Gly-63 to Ser-73.
745750	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 522 as residues: Ser-2 to Glu-17.
746285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 523 as residues: Lys-87 to Lys-92.
746416	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 524 as residues: Arg-6 to Leu-12, Tyr-18 to Asp-25.
747851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 525 as residues: Gly-124 to Ser-129, Leu-162 to Gly-167, Val-272 to Ala-278, Lys-293 to Asp-298.
751315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 527 as residues: Cys-12 to Pro-20.
754634	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 529 as residues: Asp-1 to Thr-10.
756833	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 531 as residues: Thr-36 to Pro-49, Glu-52 to Pro-67.
756878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 532 as residues: Pro-8 to Lys-15, Gly-69 to Trp-75.
757332	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 533 as residues: Gln-23 to Val-31, Phe-39 to Ile-52.
760835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 534 as residues: Phe-1 to Lys-7, Cys-82 to Ser-90.
761760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 535 as residues: Arg-34 to Pro-39, Gly-43 to Asp-51, Gln-147 to Arg-153.
762520	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 536 as residues: His-6 to His-11, Ala-13 to Glu-18, Ala-60 to Ser-65, Ile-72 to Ser-77, Gln-95 to Phe-101, Leu-136 to Ser-142.
764461	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 537 as residues: Val-15 to Ala-22, Val-26 to Gly-38.
764517	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 538 as residues: Gly-30 to Lys-36, Gly-94 to Ala-100, Gln-150 to Gly-156, Gln-189 to Leu-195.
765132	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 539 as residues: Asn-80 to Thr-87, Ser-165 to Leu-182, Thr-196 to His-201, Lys-271 to His-279, Asp-286 to Gly-292, Tyr-294 to Leu-302.
765667	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 540 as residues: Pro-14 to Pro-21, Pro-30 to Pro-36.

767113	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 541 as residues: Ala-62 to Pro-73, Pro-75 to Thr-83, Thr-110 to Phe-115, Glu-142 to Asp-150, Gln-158 to Ser-167, Glu-182 to Thr-187, Ser-190 to Asp-204.
767204	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 542 as residues: Ala-22 to Met-29, Arg-45 to Phe-56, Asp-63 to Asp-71, Gly-81 to Ala-88, Gln-155 to Trp-162.
767962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 544 as residues: Glu-126 to Gly-132, Asn-146 to Ser-158, Phe-179 to Leu-188.
768040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 545 as residues: Pro-24 to Trp-32, Val-51 to Arg-62, Gly-84 to Asp-93, Asp-108 to Asn-120, Glu-150 to Val-158, Gly-169 to Gly-175.
769956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 546 as residues: Pro-1 to Arg-6.
770133	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 547 as residues: Glu-1 to Ser-6.
771964	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 549 as residues: Pro-8 to Gly-15, Thr-26 to Phe-32, Thr-102 to Ser-109, Ala-112 to Thr-118, His-130 to Glu-152, Ser-161 to Ala-170, Ser-204 to His-209, Gly-221 to Ser-229, Ser-233 to Ala-240, Glu-242 to Pro-247, Leu-251 to Gln-258, Leu-278 to Leu-285, Thr-333 to Glu-338.
773387	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 551 as residues: Lys-36 to Lys-45, Ala-59 to Arg-67, Cys-99 to Arg-108, Ala-115 to Cys-125, Arg-143 to Arg-153.
773827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 552 as residues: Pro-1 to Ala-15, Ser-72 to His-79, Gly-89 to Tyr-105, Lys-179 to Lys-184, Arg-246 to Asp-251, Glu-302 to Lys-309, Ser-329 to Phe-341.
774108	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 553 as residues: Ala-1 to Gly-21, Pro-28 to Leu-39, Pro-48 to Asp-62, Arg-71 to Arg-78.
775339	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 555 as residues: Asp-6 to Thr-13, Asp-24 to Met-30.
775582	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 556 as residues: Gly-1 to Asn-12, Ser-69 to Glu-77.
777809	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 558 as residues: Arg-15 to Gly-25.
778927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 559 as residues: Ala-74 to Ser-82, Asn-109 to Ala-124, Ser-147 to Ile-152, Pro-188 to Gly-194, Arg-290 to Pro-299, Tyr-307 to Glu-319, Tyr-341 to Ile-346, Lys-423 to Ser-441, Gln-452 to Glu-465.
779262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 560 as residues: Arg-5 to Ile-24, Gly-35 to Trp-40, Glu-42 to Thr-48, Lys-76 to Gly-95.
780149	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 562 as residues: Gly-13 to Gln-18, Pro-71 to Glu-89, Ile-134 to Asp-139, Pro-232 to Met-240.
780583	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 563 as residues: Asn-58 to Thr-64, Ile-72 to Ser-78, Gly-119 to Lys-128.
780960	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 564 as residues: Ala-7 to Ile-14, Lys-27 to Asp-35, Thr-63 to Leu-73.
781469	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 565 as residues: Pro-1 to Ala-12, Arg-27 to Gln-45, Arg-57 to Gln-64, Lys-74 to Asp-96.
781771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 567 as residues: Glu-38 to Leu-52, Glu-64 to Lys-72, Asn-92 to Ala-102, Ala-104 to Asp-119, Pro-121 to Pro-130, Ser-165 to Ser-173.
782033	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 568 as residues: Ala-1 to Gly-19, Gln-41 to Gly-46.
782105	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 569 as residues: Leu-13 to Gly-34, Arg-77 to Pro-85, Lys-129 to Arg-135.
782122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 570 as

	residues: Pro-1 to Arg-6, Ala-102 to Ala-108, Pro-148 to Asp-158, Gly-164 to Ala-171, Pro-223 to Asn-231, Pro-272 to Ser-282, Ala-294 to Pro-310, Pro-322 to Arg-327.
783245	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 572 as residues: Leu-90 to Arg-97, Ala-107 to Pro-113.
783247	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 573 as residues: Ser-2 to Leu-8.
783413	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 574 as residues: Lys-33 to Val-39.
784407	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 575 as residues: Gly-28 to Val-36.
784548	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 576 as residues: Trp-1 to Pro-9, Pro-15 to Gln-24, Pro-52 to Thr-57.
785677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 578 as residues: Gly-7 to Gly-14.
786238	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 579 as residues: Gly-1 to Gly-8.
786389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 580 as residues: Ser-2 to Arg-16, Gly-34 to Glu-44, Arg-62 to Gln-69, Pro-102 to Ile-108, Asp-187 to Thr-193, Leu-203 to Pro-213.
786929	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 581 as residues: Pro-2 to Trp-7, Tyr-36 to Tyr-43.
786932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 582 as residues: Ser-18 to His-30, Thr-39 to Arg-51, Leu-59 to Thr-66, Pro-131 to Lys-136, Pro-149 to Ser-157.
787078	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 583 as residues: Glu-20 to Pro-26.
787283	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 585 as residues: Glu-7 to Arg-13, Gln-26 to Arg-34.
788988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 587 as residues: Pro-41 to Tyr-50, Thr-70 to Lys-75.
789092	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 588 as residues: Thr-27 to Ala-34, Leu-41 to Glu-48, Glu-76 to Asn-87, Asn-110 to Leu-118, Gly-125 to Lys-133.
789298	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 589 as residues: Arg-1 to Ser-14, Glu-56 to Gly-61, Ala-92 to Gln-98, Glu-134 to Val-154.
789718	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 591 as residues: Cys-17 to Ala-24.
790285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 594 as residues: Thr-11 to Leu-18, Leu-22 to Val-31, Trp-33 to Lys-49, Ser-63 to Glu-72, Cys-80 to Ala-91, Pro-97 to His-116.
790509	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 595 as residues: Ser-6 to His-20, Leu-22 to Gly-32, Lys-103 to Arg-111, Ser-125 to Gly-130, Glu-204 to His-210, Thr-213 to His-219, Pro-222 to Asp-244, Ser-250 to Glu-258, Arg-263 to Arg-268.
790775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 596 as residues: Arg-42 to Asp-48, Cys-79 to Thr-85, Leu-113 to Ser-123.
790888	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 597 as residues: Pro-14 to Asp-19, Asp-40 to Leu-45, Ser-53 to Val-58, Leu-81 to Tyr-91.
791506	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 598 as residues: Arg-1 to Gly-9, Asp-19 to His-25, Gly-51 to Glu-61.
792002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 601 as residues: Arg-1 to Gly-6, Val-22 to Pro-35, Val-106 to Ile-112, His-118 to Gln-124, Ser-132 to Leu-145, Asn-164 to Asn-170, Arg-187 to Tyr-192.
792291	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 602 as residues: Pro-14 to Arg-31.
792371	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 603 as

	residues: Gly-37 to Gly-52, Pro-63 to Gly-69, Ser-74 to His-81, Ser-94 to Thr-105, Val-109 to Thr-114, Phe-165 to Ser-181, Ala-191 to Asp-196, Asn-209 to Ser-216.
792660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 604 as residues: Thr-11 to Arg-16, Asn-78 to Asp-84.
792782	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 605 as residues: Ala-65 to Gly-81.
792890	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 606 as residues: Pro-26 to His-31, Arg-34 to Ser-44, Pro-59 to Ser-71, Leu-77 to Gly-83.
792931	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 607 as residues: Pro-3 to His-12.
792943	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 608 as residues: Lys-3 to Tyr-9, Gly-15 to Thr-22, Leu-36 to Asp-41, Leu-67 to Lys-76, Asp-86 to Ser-93, Tyr-174 to Asp-184, Leu-255 to Glu-260, Ile-331 to Val-337.
793446	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 611 as residues: His-1 to Gly-12.
793639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 612 as residues: Arg-6 to Arg-13, Pro-47 to Val-52, Gln-57 to Arg-65, Arg-72 to Glu-78, Asp-117 to Thr-124, Phe-132 to His-137.
794213	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 613 as residues: Tyr-1 to Trp-9, Thr-44 to Leu-49.
795955	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 615 as residues: Lys-60 to Lys-65, Lys-99 to Ala-104.
796555	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 617 as residues: Ser-1 to Gly-10, Gly-90 to Gly-97, Asn-185 to Arg-197, Pro-202 to Arg-211.
796675	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 618 as residues: Ser-35 to Gly-40, Ser-103 to His-109, Tyr-151 to Gly-159, Pro-216 to Glu-224, Asn-249 to Trp-258, Pro-278 to Glu-284.
796743	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 619 as residues: Asn-1 to Gly-6, Asn-100 to Glu-106, Gln-108 to Asp-116, Asp-146 to Thr-151, Thr-191 to Glu-198.
796792	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 620 as residues: Asn-23 to Gly-28, Cys-41 to Asp-47, Gln-82 to Glu-88.
799668	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 621 as residues: Gly-2 to Arg-10, Ile-27 to Pro-33.
799669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 622 as residues: Gly-1 to Ser-12.
799673	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 623 as residues: Gly-1 to Ala-14, Leu-38 to Pro-46.
799674	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 624 as residues: Pro-39 to Pro-45.
799678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 625 as residues: Lys-54 to Ser-60, Tyr-86 to His-93.
799728	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 626 as residues: Trp-7 to Gln-19.
799748	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 627 as residues: Glu-7 to Arg-12, Lys-62 to His-68.
799760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 628 as residues: Ile-15 to Trp-22.
800296	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 630 as residues: Asn-19 to Thr-39, Glu-42 to Ile-48, Arg-55 to Asp-66, Ile-130 to Arg-135, Lys-149 to Ala-156, Glu-166 to Leu-176, Met-213 to Lys-219, Pro-233 to Pro-248, Lys-258 to Lys-263.
800327	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 631 as residues: Arg-13 to Gly-19, Lys-32 to Glu-39, Lys-94 to Trp-100, Asn-102 to Asp-108, Ala-117 to Leu-129.
800816	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 632 as

	residues: Lys-1 to Ile-11, Gln-36 to Leu-46.
800835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 633 as residues: Trp-1 to Gln-11, Gly-37 to Gln-50, Ser-109 to Gln-114, Glu-146 to Leu-155, Glu-175 to Gly-180, Thr-188 to Ser-200.
805429	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 634 as residues: Pro-6 to Ser-51, Gln-100 to Glu-107.
805458	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 635 as residues: Glu-57 to Ser-62, Thr-102 to Ser-120.
805478	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 636 as residues: Glu-31 to Glu-37, Pro-47 to Ser-52, Asn-57 to Asn-66.
805805	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 637 as residues: Arg-1 to Cys-16, Tyr-59 to Lys-68, Glu-76 to Arg-82.
806486	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 638 as residues: Phe-1 to Val-6, Pro-11 to Gly-18.
806498	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 639 as residues: Pro-6 to Ser-17, Arg-81 to Thr-88, Arg-198 to Val-203, Arg-285 to Arg-296, Gln-302 to Ser-361, Leu-399 to Ser-407.
810870	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 641 as residues: Val-12 to Ile-21.
811730	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 642 as residues: Arg-33 to Arg-40.
813262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 645 as residues: Gly-31 to Asp-51, Cys-68 to Val-81, Leu-85 to Cys-92.
815637	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 646 as residues: Arg-13 to Asp-19, Ser-80 to Gly-91, Pro-99 to Ser-111.
815853	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 647 as residues: Cys-25 to Ser-31, Gln-63 to Asp-73, Arg-98 to Gly-106, Pro-120 to Arg-125, Leu-136 to Asp-141, Gly-155 to Glu-170, Phe-179 to Gly-186.
815999	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 648 as residues: Asp-1 to Asp-10, Arg-19 to Glu-28, Gly-86 to Leu-93, Arg-113 to His-118.
823427	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 649 as residues: Pro-16 to Cys-27, Arg-70 to Arg-76.
823704	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 650 as residues: Val-29 to Lys-34, Arg-58 to His-63, Gln-87 to Lys-97, Arg-195 to Ser-200.
824798	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 651 as residues: Thr-28 to His-34.
825018	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 652 as residues: Gln-1 to Asn-11, Leu-19 to Thr-24, Lys-47 to Arg-55, Lys-94 to Asp-99, Ala-101 to Arg-107, Ala-137 to Tyr-146, Gln-150 to Ser-163, Gly-169 to Lys-175, Thr-182 to Ala-189, Glu-249 to Ser-258, Pro-266 to Tyr-275, Tyr-285 to Gly-298, Asp-302 to Gln-315, Tyr-318 to Thr-325, Gln-332 to Ala-359, Ser-372 to Phe-384, Leu-390 to Ala-399, Ala-428 to Arg-437.
825787	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 654 as residues: Pro-21 to Leu-28, Arg-40 to Ile-49, Asp-84 to Asn-93, Arg-124 to Asn-130, Gly-140 to Asn-145, Leu-187 to Gln-196, Pro-208 to Asp-213, Arg-244 to Asp-252, Ile-325 to Gln-336, Glu-372 to Ala-379, Asn-435 to Leu-446, Ala-460 to Arg-467, Val-500 to Asp-506, Lys-524 to Asn-533, Thr-592 to Lys-598, Asp-648 to Ser-656.
826116	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 655 as residues: Glu-20 to Cys-35.
826147	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 656 as residues: Lys-18 to Leu-24.
827586	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 658 as residues: Ser-7 to Gly-14, Leu-22 to Ala-28, Thr-57 to Ser-62.
827735	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 660 as residues: Pro-2 to Ser-12, Gln-25 to Glu-31, Val-40 to Arg-45.
827740	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 661 as

	residues: Ile-22 to Lys-28.
827808	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 662 as residues: Glu-2 to Gln-13, Gln-20 to Gly-29, Arg-32 to Cys-47, Pro-54 to Trp-61, Thr-73 to Gln-91, Gly-96 to Ser-103.
828357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 664 as residues: Gly-1 to Gly-10, Val-25 to Glu-32, His-67 to Arg-73.
828612	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 666 as residues: Asp-25 to Gln-31, Asp-36 to Tyr-41, Gln-43 to Thr-48, Lys-71 to Thr-76.
828647	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 667 as residues: Ser-2 to Ser-8, Arg-61 to Gln-74, Ser-192 to Asn-202, Gln-229 to Lys-236, Gly-281 to Gly-292, Glu-333 to Ala-345, Ala-352 to Gln-358, Glu-360 to Leu-366, Asp-443 to Ser-449, Glu-452 to Glu-459, Asp-485 to Thr-492, Ala-510 to Gln-516, Ala-545 to Ala-552, Leu-560 to Thr-566, Glu-586 to Ala-592, Asp-601 to Gln-607, Leu-609 to Leu-620.
828698	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 668 as residues: Pro-28 to Ser-43, Pro-45 to Ala-50, His-58 to Gln-63.
828962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 669 as residues: Ala-42 to Gly-49, Thr-54 to Cys-63.
829282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 671 as residues: Ser-7 to Gln-12, Gly-25 to Gly-31, Gly-71 to Gly-84, Leu-147 to Glu-164, Trp-172 to Leu-180.
829368	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 672 as residues: Glu-1 to Tyr-7, Pro-13 to Glu-24, Arg-31 to Ile-39, Gln-59 to Lys-65, His-67 to Leu-74.
829751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 673 as residues: Ala-29 to Arg-45, Ser-48 to Glu-59, Lys-73 to Trp-79, Ala-100 to Ser-109.
829934	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 675 as residues: Arg-1 to Arg-6, Ser-46 to Asp-71, Glu-76 to Glu-90, Gln-107 to Tyr-118, Ser-124 to Asp-131, Glu-163 to Asp-170, Ala-239 to Asp-245, Asp-262 to Arg-268, Gln-276 to Asp-283, Arg-293 to Lys-300, Ser-307 to Glu-313, Phe-346 to Phe-351, Phe-361 to Ala-373.
829951	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 677 as residues: Thr-21 to Lys-28.
830173	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 678 as residues: Gly-51 to Asn-68, Thr-75 to Lys-82, Ala-86 to Ala-97, Asn-99 to Arg-106, Leu-121 to Phe-126, Ala-155 to Ser-163, Asp-175 to Asp-180, Ala-184 to Phe-196, Leu-204 to Asn-214, Asp-219 to Gln-232, Leu-269 to Arg-274, Pro-392 to Pro-400, Thr-430 to Asn-437, Tyr-472 to Gln-477, Leu-483 to Gln-499, Asn-516 to Gln-524, Ser-533 to Gln-546, Lys-562 to Glu-576, Leu-589 to Ala-594, Asp-624 to Ala-633, Ile-741 to Asp-746, Val-817 to Lys-839, Tyr-872 to Lys-878, Thr-929 to Asp-940.
830365	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 680 as residues: Trp-36 to Glu-41, Asp-71 to Arg-76, Asn-80 to Gly-87, Arg-103 to Pro-115.
830456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 681 as residues: Leu-48 to Cys-54.
830549	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 682 as residues: Ser-1 to Pro-24, Pro-40 to Thr-50, Glu-62 to Gly-83, Arg-103 to Leu-108, Ser-141 to Lys-146, Lys-184 to Ser-190.
830602	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 683 as residues: Arg-53 to Thr-63, Ile-100 to Lys-108.
830610	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 684 as residues: Pro-27 to Cys-32, Ala-61 to Gly-70, Pro-76 to Gly-85, Met-115 to Gly-120, Glu-162 to Lys-171, Pro-222 to Tyr-228, Glu-242 to Thr-248, Lys-261 to Gly-269.
830644	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 685 as residues: Ile-1 to Ser-10.
830707	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 686 as residues: Asn-34 to Leu-53, Gln-61 to Leu-67.

830709	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 687 as residues: Arg-13 to Gln-18, Pro-22 to Ala-40, Ala-66 to Asp-84, Glu-94 to Arg-101.
830733	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 688 as residues: Glu-1 to Asp-8.
830855	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 690 as residues: Ser-1 to His-6.
830949	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 691 as residues: Arg-5 to Arg-12, Gly-25 to Trp-30, Thr-77 to Trp-96, Thr-101 to Glu-106, Gly-109 to Arg-127.
830965	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 692 as residues: Leu-24 to Arg-56, Pro-83 to Arg-90, Ile-110 to Ile-115, Lys-123 to Val-136.
830973	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 693 as residues: Ser-1 to Asn-7, Tyr-13 to Asp-23.
830989	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 695 as residues: Cys-2 to Ser-16, Glu-55 to Lys-61, Pro-83 to Leu-88, Ser-135 to Pro-148, Val-152 to Arg-163, Pro-223 to Thr-230, Ala-242 to Val-253, Arg-258 to Glu-274, Gly-290 to Asp-300, Lys-337 to Asn-345, Asp-373 to Ala-398, Gly-401 to Lys-406, Gln-410 to Ala-430, Pro-433 to Gln-460.
831134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 696 as residues: Ala-19 to His-24.
831200	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 697 as residues: Trp-1 to Gly-6.
831531	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 699 as residues: Ser-94 to Asn-116, Glu-139 to Asp-155, Tyr-190 to Leu-195, Ile-230 to Ile-235, Ser-309 to Glu-317.
831665	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 700 as residues: Leu-4 to Trp-12.
831724	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 701 as residues: Pro-26 to Lys-32.
831884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 702 as residues: Pro-46 to Ala-52, Thr-68 to Trp-86, Arg-91 to Arg-96, Lys-127 to Asp-141.
831897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 703 as residues: Pro-10 to Ser-20, Val-73 to Ser-78, Asp-123 to Glu-134, Leu-138 to Val-149, Ala-181 to Ala-187, Thr-189 to Val-196, Arg-213 to Gln-224.
831922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 704 as residues: Leu-32 to Asp-37, Ile-43 to Asn-49.
832266	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 707 as residues: Ala-73 to Arg-79.
832309	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 708 as residues: Val-10 to Gly-15, Ser-98 to Thr-105.
832342	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 709 as residues: Pro-9 to Trp-16, Thr-66 to Ser-72.
832351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 710 as residues: Asp-16 to Val-21, Leu-54 to Asp-71.
832352	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 711 as residues: Asp-16 to Val-21, Leu-33 to Asp-50.
832434	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 712 as residues: Tyr-15 to Glu-23, Ser-46 to Arg-51, Gln-56 to Trp-61, Pro-79 to Lys-86.
832490	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 713 as residues: Arg-16 to Gly-23, Ala-37 to Asp-46, Asp-91 to Asp-97.
832573	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 714 as residues: Ala-9 to Gln-16, Glu-21 to Arg-27, Gly-66 to Pro-72.
833394	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 716 as residues: Glu-1 to Gly-6, Asp-12 to Gly-22, Ile-28 to Gln-33, Cys-86 to Gly-92, Gly-96 to Ile-105.
835355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 717 as

	residues: Glu-8 to Ser-15, Gly-42 to Leu-49, Pro-73 to Gly-79, Tyr-82 to Arg-87, Ser-109 to Gly-118, Glu-122 to Ile-128, Asp-132 to Gly-137, Asp-146 to Arg-151, Pro-153 to Lys-158, Gly-191 to His-197, Tyr-210 to Ser-218, Lys-234 to Gly-239, Ala-246 to Ala-252, His-257 to Pro-268, Ser-274 to Gly-280, Pro-316 to Tyr-323, Ile-358 to Leu-363, Gln-375 to Tyr-381, Gln-390 to Tyr-397, Gln-418 to Cys-430.
835497	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 718 as residues: Glu-141 to Pro-151, Asp-179 to Glu-184, Gly-214 to Ser-219, Thr-226 to Tyr-231, Thr-239 to Gly-248, Pro-281 to Gly-297, Pro-326 to Arg-336, Gln-408 to Asp-416.
835978	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 720 as residues: Trp-25 to Val-31.
836274	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 722 as residues: Ser-1 to Glu-9.
836731	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 723 as residues: Lys-15 to Glu-22, Gly-25 to Ala-34, Glu-75 to Gly-81, Gln-91 to Val-100, Pro-146 to Glu-155, Gln-161 to Phe-167, Asn-170 to Gly-178.
838014	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 724 as residues: Arg-1 to Pro-10, Asp-170 to Pro-176, Arg-203 to Tyr-212, Gly-228 to Lys-235.
838874	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 725 as residues: Gln-30 to Gln-45.
839120	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 726 as residues: Thr-22 to Arg-27, Arg-69 to Gly-75, Leu-77 to Pro-85.
839611	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 727 as residues: Asp-12 to Thr-17.
840138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 728 as residues: Ser-1 to Thr-10.
840616	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 729 as residues: Lys-93 to Gly-99, Glu-144 to Leu-160, Ser-265 to Asp-270, Thr-382 to Gln-396, Val-512 to Val-517, Glu-519 to Asp-535.
840780	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 730 as residues: Leu-8 to Gly-14, Pro-151 to Glu-157.
840857	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 731 as residues: Gln-7 to Glu-22, Ala-27 to Arg-46, Ser-138 to Lys-147, Lys-158 to Pro-163, Asn-171 to Glu-187, Glu-202 to Val-208, Glu-234 to Gly-240, Ser-253 to Lys-260, Gln-272 to Pro-279, Arg-292 to Glu-307, Arg-310 to Arg-317, Asp-342 to Gly-351, Pro-367 to Gly-375, Pro-378 to Arg-388, Leu-425 to Ala-447, Arg-536 to Asp-544, Lys-551 to Lys-561, Val-599 to Asp-604, Ser-622 to Ala-630, Pro-653 to Phe-659, Thr-666 to Ile-673, Pro-699 to Phe-705, Asn-709 to Gly-719, Ala-725 to Phe-737.
840862	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 732 as residues: Arg-2 to Pro-12, Lys-32 to Asn-37, His-75 to Asn-82.
840864	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 733 as residues: Pro-17 to Arg-30, Cys-34 to Gly-40, Met-74 to Glu-81, Pro-106 to Asp-111, Val-136 to Cys-147, Asn-192 to Asp-198.
840938	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 735 as residues: Ser-140 to Thr-148, Thr-194 to Lys-202.
841884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 736 as residues: Thr-34 to Glu-47.
842241	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 737 as residues: Thr-92 to Lys-101, Glu-134 to Thr-142, Glu-149 to Lys-155, Trp-179 to Ser-187, Thr-205 to Arg-211, Ser-218 to Tyr-225, Asp-283 to Gln-290, Glu-292 to Ile-302, Asn-304 to Met-315.
843712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 738 as residues: Arg-10 to Asn-16, Ala-59 to Pro-67.
844040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 739 as residues: Phe-59 to Glu-68, Lys-105 to Gly-111.
844617	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 742 as

	residues: Arg-1 to Lys-7.
846187	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 745 as residues: Gly-8 to Gly-14, Gly-41 to Glu-48, Glu-54 to Lys-74, Glu-87 to Arg-98, Thr-158 to Asn-166, Gly-247 to Ser-254, Gly-257 to Arg-277, Ala-437 to Ser-444, Lys-505 to Arg-510, Phe-519 to Tyr-525, Lys-531 to Pro-538, Gly-562 to Leu-571, Phe-606 to Val-613, Val-692 to Ala-697, Ser-705 to Leu-715, Leu-742 to Cys-747.
HANGA53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 749 as residues: Arg-4 to Ser-9.
HAHCP93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 752 as residues: Ser-1 to Ser-12, Thr-23 to Arg-28.
HBGAA76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 753 as residues: Ser-4 to Ser-11, Pro-27 to Asn-37.
HTXPI29R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 756 as residues: Thr-17 to Leu-24, Thr-57 to Tyr-67, Leu-92 to Phe-102, Asn-128 to Gln-134.
HBGAA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 760 as residues: Arg-62 to Leu-70, Ile-74 to Arg-79.
HDPJR77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 763 as residues: Glu-7 to Lys-22, Thr-33 to Glu-39, Lys-69 to Glu-76, Asp-84 to Tyr-90.
HTTIO41R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 764 as residues: Val-17 to Ser-22, Arg-41 to Glu-46, Lys-50 to Pro-75, Ser-92 to Pro-100.
HDPUL86R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 767 as residues: Lys-7 to Gly-13.
HTXNT16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 768 as residues: Leu-67 to Asn-72, Thr-102 to Phe-111, Gly-127 to Gln-135.
HLXNA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 770 as residues: Gln-1 to Glu-6, Pro-23 to Trp-31, Arg-46 to Trp-51.
H2LAX93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 772 as residues: Glu-3 to Gln-10.
HWAFW10R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 773 as residues: Glu-13 to Asp-22, His-34 to Trp-40, Arg-69 to Lys-75.
HBGDD17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 775 as residues: Arg-23 to Thr-28, Pro-40 to Glu-51, Ala-62 to His-68.
H2CBB43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 778 as residues: Asp-90 to Asp-95, Arg-106 to Thr-117.
H2CBQ77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 779 as residues: Asp-11 to Gly-16, Gln-19 to Tyr-24, Pro-34 to Gly-46.
HOEMK06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 781 as residues: Pro-1 to Gln-14.
HCHAG30R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 783 as residues: Gly-1 to Trp-7.
HAEAI26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 788 as residues: Lys-32 to Val-40, Arg-43 to Pro-51.
H2CBN76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 791 as residues: Ala-17 to Leu-22, Thr-72 to Lys-77.
HAGFX49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 792 as residues: Ala-10 to Leu-15, His-64 to Cys-71.
HTXKR32R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 794 as residues: Ser-2 to Gly-12, Glu-57 to Val-65.
H6EAF46R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 796 as residues: Arg-11 to Ser-21.
H2LAK40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 798 as residues: Glu-11 to Lys-20, Pro-22 to Arg-28.
H2LAY71R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 799 as residues: Arg-26 to Leu-36, Gln-82 to Asp-101, Arg-103 to Arg-108, Arg-113 to Arg-131.
HASAW80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 803 as

	residues: Gly-1 to Arg-6, Ala-19 to Pro-27, Gly-34 to Phe-40.
HCHAF25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 804 as residues: Ser-30 to Thr-40, Leu-78 to Val-85, Asp-92 to Ala-97.
HLTHH84R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 805 as residues: Glu-2 to Ala-8.
HADDC09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 808 as residues: Leu-3 to Gly-9, Thr-20 to Gly-29.
HAQAI10R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 811 as residues: Gly-1 to Lys-21.
HBGBT78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 814 as residues: Asn-1 to Lys-22.
HBGCB06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 815 as residues: Phe-1 to Phe-15.
HCHMW05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 823 as residues: Pro-6 to Ser-11.
HODFW25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 829 as residues: Ser-1 to Thr-8, Glu-17 to Ala-32, Arg-39 to Trp-47.
HOEMQ91R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 830 as residues: Arg-8 to Ser-13.
HOGBG56R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 831 as residues: Lys-20 to Arg-25.

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at

least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice

are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention , and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995).

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for

immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., Proc. Natl. Acad. Sci. USA 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al.,

Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include,

but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast,

higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. *See*, Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to

the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the

polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (*see, e.g.*, Carter *et al., Nucl. Acids Res. 13*:4331 (1986); and Zoller *et al., Nucl. Acids Res. 10*:6487 (1982)), cassette mutagenesis (*see, e.g.*, Wells *et al., Gene 34*:315 (1985)), restriction selection mutagenesis (*see, e.g.*, Wells *et al., Philos. Trans. R. Soc. London SerA 317*:415 (1986)).

The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased

solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000; 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500; 14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a

reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-

304 (1992); Francis *et al., Intern. J. of Hematol. 68*:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992).

The breast/ovarian cancer antigen polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present

invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention

contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the

invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide seuqence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide

components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hyrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG,

IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that

specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6}M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, $^{10-12}$ M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or $^{10-15}$ M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferrably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol.

Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to

induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by

fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any

desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein

Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent

No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be

assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework

regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not

limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or

factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS,

MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.),

Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or

portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using

methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent

materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical

chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York,

which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of

the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities

include those with a dissociation constant or Kd less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6} M, 5 X 10^{-7} M, 10^{-7} M, 5 X 10^{-8} M, 10^{-8} M, 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, 10^{-12} M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, and 10^{-15} M.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989).

In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the

host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method

known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that

expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral

routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al.,

J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form

of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend

on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the

amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule

is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface- bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The breast/ovarian cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the

invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention provides a method of detecting increased or decreased expression levels of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides in affected individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer, involving measuring the expression level of breast/ovarian cancer antigen polynucleotides in breast and/or ovarian tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer.

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression will experience a

worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of breast, ovarian, breast cancer and/or ovarian cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating the level of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the level of the mRNA encoding the breast, ovarian, breast cancer and/or ovarian cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in a second biological sample). Preferably, the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the female reproductive system related disorder or being determined by averaging levels from a population of individuals not having a female reproductive system related disorder. As will be appreciated in the art, once a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as vaginal pool, breast milk, lymph, sera, plasma, urine, semen, synovial fluid and spinal fluid) which contain the breast, ovarian, breast cancer and/or ovarian cancer polypeptide, breast and/or ovarian tissue, and other tissue sources found to express the breast, ovarian, breast cancer and/or ovarian cancer polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferrably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with breast, ovarian, breast cancer and/or ovarian cancer polynucleotides attached may

be used to identify polymorphisms between the breast, ovarian, breast cancer and/or ovarian cancer polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, though most preferably in breast and/or ovarian related proliferative, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses breast, ovarian, breast cancer and/or ovarian cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L.Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of hematopoietic

cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a breast/ovarian cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed

on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to breast, ovarian, breast cancer and/or ovarian cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample.

Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, breast, ovarian, breast cancer and/or ovarian cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., vaginal pool, breast milk, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or

antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer polypeptide of the present invention in cells or body fluid of an individual, or more preferrably, assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer of the present invention in breast and/or ovarian cells or vaginal pool or breast milk of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, breast/ovarian cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, preferably proliferative disorders of the breast and/or ovary, and/or cancerous disease and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing

inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996);